"UTILITY OF VARIOUS TWO DIMENSIONAL ECHOCARDIOGRAPHIC AND ANGIOGRAPHIC FEATURES TO DIFFERENTIATE PRIMARY FROM SECONDARY PULMONARY HYPERTENSION"

DISSERTATION SUBMITTED FOR

D.M. DEGREE EXAMINATION
BRANCH II - CARDIOLOGY

MADRAS MEDICAL COLLEGE
AND
GOVERNMENT GENERAL HOSPITAL
CHENNAI – 600003

THE TAMILNADU DR.M.G.R.MEDICAL UNIVERSITY
CHENNAI – 600032

AUGUST 2009

"learn to heal"

CERTIFICATE

This is to certify that the dissertation entitled **"UTILITY OF VARIOUS TWO DIMENSIONAL ECHOCARDIOGRAPHIC AND ANGIOGRAPHIC FEATURES TO DIFFERENTIATE PRIMARY FROM SECONDARY PULMONARY HYPERTENSION"** is the bonafide original work of **Dr.P.K. JAWAHARLAL** in partial fulfillment of the requirements for D.M. Branch-II (CARDIOLOGY) examination of THE TAMILNADU DR.M.G.R. MEDICAL UNIVERSITY to be held in August 2009.The period of post-graduate study and training was from August 2006 to July 2009.

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DECLARATION

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Department : cardiology, GGH, ch-3.

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INTRODUCTION

Pulmonary hypertension

Pulmonary hypertension is an increase in blood pressure in the pulmonary artery, pulmonary vein, or pulmonary capillaries leading to shortness of breath, dizziness, fainting, and other symptoms, all of which are exacerbated by exertion. It was first identified by Dr. Ernst Von Romberg in 1891 according to the most recent classification, it can be one of five different types: *arterial, venous, hypoxic, thromboembolic* or *miscellaneous*.

Signs and symptoms

Common symptoms are shortness of breath, fatigue, non-productive cough, angina pectoris, fainting or syncope, peripheral edema and rarely hemoptysis .Pulmonary *arterial* hypertension (PAH) typically does not present with orthopnea or paroxysmal nocturnal dyspnea, while pulmonary *venous* hypertension typically does.

Diagnosis

Because pulmonary hypertension can be of five major types, a series of tests must be performed to distinguish pulmonary *arterial* hypertension from *venous*, *hypoxic*, *thomboembolic*, or *miscellaneous* varieties.

A physical examination is performed to look for typical signs of pulmonary hypertension. These include widely split S_2, a loud P_2, parasternal heave, possible S_3 or third heart sound, and pulmonary regurgitation. Other signs include an elevated jugular venous pressure, peripheral edema ,ascites, hepatojugular reflux, and clubbing.

Further procedures are required to confirm the presence of pulmonary hypertension and exclude other possible diagnoses. These generally include pulmonary function tests, blood tests to exclude HIV, autoimmune diseases, and liver disease, electrocardiography (ECG), arterial blood gas measurements, X-rays of the chest (followed by high-resolution CT scanning if interstitial lung disease is suspected), and ventilation-perfusion or V/Q scanning to exclude chronic thromboembolic pulmonary hypertension. Clinical improvement is often measured by a "six-minute walk test", i.e. the distance a patient can walk in six minutes. . Blood BNP level is also being used now to follow progress of patients with pulmonary hypertension.

Diagnosis of PAH requires the presence of pulmonary hypertension with two other conditions. Pulmonary artery occlusion pressure (PAOP or PCWP) must be less than 15 mm Hg (2000 Pa) and pulmonary vascular resistance (PVR) must be greater than 3 Wood units (240 dyn•s•cm^{-5} or 2.4 mN•s•cm^{-5}).

Although pulmonary arterial pressure can be estimated on the basis of echocardiography, pressure measurements with a Swan-Ganz catheter provides the most definite assessment.

Normal pulmonary arterial pressure in a person living at sea level has a mean value of 12–16 mm Hg . Pulmonary hypertension is present when mean pulmonary artery pressure exceeds 25 mm Hg (3300 Pa) at rest or 30 mm Hg (4000 Pa) with exercise.

Mean pulmonary artery pressure (mPAP) should not be confused with systolic pulmonary artery pressure (sPAP), which is often reported on echocardiogram reports. A systolic pressure of 40 mm Hg typically implies a *mean* pressure more than 25 mm Hg. Roughly, mPAP = 0.61•sPAP + 2.

Causes and classification

The Venice 2003 Revised Classification system can be summarized as follows

WHO Group I - Pulmonary arterial hypertension

- Idiopathic (IPAH)
- Familial (FPAH)
- Associated with other diseases (APAH): collagen vascular disease (e.g. scleroderma), congenital shunts between the systemic and pulmonary circulation, portal hypertension, HIV infection, drugs, toxins, or other diseases or disorders
- Associated with venous or capillary disease

- WHO Group II - Pulmonary hypertension associated with left heart disease
  - Atrial or ventricular disease
  - Valvular disease (e.g. mitral stenosis)
- WHO Group III - Pulmonary hypertension associated with lung diseases and/or hypoxemia

    - Chronic obstructive pulmonary disease (COPD), interstitial lung disease (ILD)
    - Sleep-disordered breathing, alveolar hypoventilation
    - Chronic exposure to high altitude
    - Developmental lung abnormalities
- WHO Group IV - Pulmonary hypertension due to chronic thrombotic and/or embolic disease
    - Pulmonary embolism in the proximal or distal pulmonary arteries
    - Embolization of other matter, such as tumor cells or parasites
- WHO Group V - Miscellaneous

Pathogenesis

Whatever the initial cause, pulmonary *arterial* hypertension (WHO Group I) involves the vasoconstriction of blood vessels connected to and within the lungs.. Over time, the affected blood vessels become both stiffer and thicker, in a process known as fibrosis. This further increases the blood pressure within the lungs and impairs their blood flow. In addition, the increased workload of the heart causes thickening and enlargement of the

right ventricle, making the heart less able to pump blood through the lungs, causing right heart failure. As the blood flowing through the lungs decreases, the left side of the heart receives less blood. This blood may also carry less oxygen than normal. Therefore it becomes harder and harder for the left side of the heart to pump to supply sufficient oxygen to the rest of the body, especially during physical activity.

Pathogenesis in pulmonary *venous* hypertension (WHO Group II) is completely different. There is no obstruction to blood flow in the lungs. Instead, the left heart fails to pumps blood efficiently, leading to pooling of blood in the lungs. This causes pulmonary edema and pleural effusions.

In hypoxic pulmonary hypertension (WHO Group III), the low levels of oxygen are thought to cause vasoconstriction or tightening of pulmonary arteries. This leads to a similar pathophysiology as pulmonary arterial hypertension.

In chronic thromboembolic pulmonary hypertension (WHO Group IV), the blood vessels are blocked or narrowed with blood clots. Again, this leads to a similar pathophysiology as pulmonary arterial hypertension.

Epidemiology

IPAH is a rare disease with an incidence of about 2-3 per million per year and a prevalence of about 15 per million. Adult females are almost three times as likely to present with IPAH than adult males. The presentation of IPAH within children is more evenly split along gender lines.

Other forms of PAH are far more common. In scleroderma the incidence has been estimated to be 6 to 60% of all patients, in rheumatoid arthritis up to 21%, in systemic lupus erythematosus 4 to 14%, in portal hypertension between 2 to 5%, in HIV about 0.5%, and in sickle cell disease ranging from 20 to 40%.

Diet pills such as Fen-Phen produced an annual incidence of 25-50 per million per year.

Pulmonary venous hypertension is exceedingly common, since it occurs in most patients symptomatic with congestive heart failure.

Up to 4% of people who suffer a pulmonary embolism go on to develop chronic thromboembolic disease including pulmonary hypertension.

Only about 1.1% of patients with COPD develop pulmonary hypertension with no other disease to explain the high pressure. Sleep apnea is usually associated with only very mild pulmonary hypertension, typically below the level of detection. On the other hand Pickwickian syndrome (obesity-hypoventilation syndrome) is very commonly associated with right heart failure due to pulmonary hypertension.

Treatment

Treatment is determined by whether the PH is arterial, venous, hypoxic, thromboembolic, or miscellaneous. Since pulmonary *venous* hypertension is synonymous with congestive heart failure, the treatment is to optimize left ventricular function by the use of diuretics, beta blockers, ACE inhibitors, etc., or to repair/replace the mitral valve or aortic valve.

In PAH, lifestyle changes, digoxin, diuretics, oral anticoagulants, and oxygen therapy are considered *conventional* therapy, but have never been proven to be beneficial in a randomized, prospective manner.

High dose calcium channel blockers are useful in only 5% of IPAH patients who are *vasoreactive* by Swan-Ganz catheter. The criteria for

vasoreactivity have changed. Only those patients whose *mean* pulmonary artery pressure falls by more than 10 mm Hg to less than 40 mm Hg with an unchanged or increased cardiac output when challenged with adenosine, epoprostenol, or nitric oxide are considered vasoreactive. Of these, only half of the patients are responsive to calcium channel blockers in the long term.

Vasoactive substances

Many pathways are involved in the abnormal proliferation and contraction of the smooth muscle cells of the pulmonary arteries in patients with pulmonary arterial hypertension. Three of these pathways are important since they have been targeted with drugs — endothelin receptor antagonists, phosphodiesterase type 5 inhibitors, and prostacyclin derivatives.

Prostaglandins

Prostacyclin (prostaglandin I_2) is commonly considered the most effective treatment for PAH. Epoprostenol (synthetic prostacyclin, marketed as Flolan) is given via continuous infusion that requires a semi-permanent central venous catheter.. Other prostanoids include. Treprostinil (Remodulin) can be given intravenously or subcutaneously, but the subcutaneous form can be very painful. Iloprost is the only inhaled form of

prostacyclin approved for use in the US and Europe. Oral and inhaled forms of Remodulin are under development. Beraprost is an oral prostanoid available in Japan and South Korea.

Endothelin receptor antagonists.

The dual (ET_A and ET_B) endothelin receptor antagonist bosentan , Sitaxentan, ambrisentan are selective endothelin receptor antagonist that blocks only the action of ET_A, Another dual/nonselective endothelin antagonist, Actelion-1, will enter clinical trials in 2008.

Phosphodiesterase type 5 inhibitors

Sildenafil, a selective inhibitor of cGMP specific phosphodiesterase type 5 (PDE5), was approved for the treatment of PAH in 2005. It is marketed for PAH as Revatio.

Surgical

Atrial septostomy is a surgical procedure that creates a communication between the right and left atria. It relieves pressure on the right side of the heart, but at the cost of lower oxygen levels in blood (hypoxia). It is best performed in experienced centers.

Lung transplantation cures pulmonary arterial hypertension, but leaves the patient with the complications of transplantation, and a post-surgical median survival of just over five years.Pulmonary thromboendarterectomy (PTE) is a surgical procedure that is used for chronic thromboembolic pulmonary hypertension. It is the surgical removal of an organized thrombus (clot) along with the lining of the pulmonary artery; it is a very difficult, major procedure that is currently performed in a few select centers. Case series show remarkable success in most patients.

Treatment for hypoxic and miscellaneous varieties of pulmonary hypertension have not been established..

Monitoring

Patients are normally monitored through commonly available tests such as:

- pulse oximetry,
- arterial blood gas tests,
- chest X-rays,
- serial ECG tests,
- serial echocardiography, and
- spirometry or more advanced lung function studies.

AIM OF THE STUDY

1) To differentiate primary PHT from secondary PHT with the use of MPI [Myocardial Performance Index] [TEI INDEX]
2) To study the effects of primary PHT and secondary PHT on right ventricular function.
3) To study the effects of primary PHT and secondary PHT on left ventricular function.
4) To study the effects of primary PHT and secondary PHT on mPAP [mean pulmonary artey pressure].
5) To study the effects of primary PHT and secondary PHT on PCWP [pulmonary capillary wedge pressure].

REVIEW OF LITERATURE

HISTORY

Presenting symptoms are effort-related. With the onset of right ventricular failure, lower extremity edema from venous congestion is characteristic. Angina is also a common symptom, generally representing more advanced disease. As the cardiac output becomes fixed and eventually falls, patients may have episodes of syncope or near-syncope. Patients with pulmonary hypertension related to left ventricular diastolic dysfunction will characteristically have orthopnea and paroxysmal nocturnal dyspnea. Patients with underlying lung disease may also report episodes of coughing. Hemoptysis is relatively uncommon in patients with pulmonary hypertension and may be associated with underlying thromboembolism and pulmonary infarction. Some patients with advanced mitral stenosis also present with hemoptysis.

PHYSICAL EXAMINATION

Large a wave in the jugular venous pulse, a low-volume carotid arterial pulse with a normal upstroke, a left parasternal (right ventricular) heave, a systolic pulsation produced by a dilated, tense pulmonary artery in

the second left interspace, an ejection click and flow murmur in the same area, a closely split second heart sound with a loud pulmonic component, and a fourth heart sound of right ventricular origin. Late in the course, signs of right ventricular failure (e.g., hepatomegaly, peripheral edema, and ascites) may be present. Patients with severe pulmonary hypertension may also have prominent v waves in the jugular venous pulse as a result of tricuspid regurgitation, a third heart sound of right ventricular origin, a high-pitched early diastolic murmur of pulmonic regurgitation, and a holosystolic murmur of tricuspid regurgitation. Tricuspid regurgitation is a reflection of right ventricular dilation. Cyanosis is a late finding. Uncommonly, the left laryngeal nerve becomes paralyzed as a consequence of compression by a dilated pulmonary artery (Ortner syndrome).

CONCOMITANT DISEASE.

Patients with scleroderma typically report Raynaud's phenomenon, dysphagia, sclerodactyly, and nonspecific arthritic symptoms. Patients with portal hypertension usually give a history of underlying chronic liver disease and may present with ascites that can be from the liver disease, right heart failure, or both. Many patients with congenital heart disease have a known history, but atrial septal defects in adults are frequently missed and patients

may have symptoms manifest only later in life. These patients often have marked cyanosis that worsens with exercise. Patients with pulmonary venous hypertension, or pulmonary hypertension associated with lung disease, can also have extreme levels of hypoxemia. In patients with chronic obstructive pulmonary disease (COPD), the clinical signs are often obscured by hyperinflation of the chest. The jugular venous pressure may also be difficult to assess in patients with COPD because of large swings in intrathoracic pressure.

DIAGNOSTIC TESTS

Laboratory tests.

If chronic arterial oxygen desaturation exists, polycythemia should be present. A number of investigators have reported hypercoagulable states, abnormal platelet function, defects in fibrinolysis, and other abnormalities of coagulation in patients with PAH. Abnormal liver function test results can indicate right ventricular failure, with resultant systemic venous hypertension.

Brain natriuretic peptide (BNP) levels are elevated in patients with pulmonary hypertension and correlate positively with the pulmonary artery pressure.

Uric acid levels are elevated in patients with pulmonary hypertension and correlate with hemodynamics. .

There is an increased incidence of thyroid disease in patients with PAH, which can mimic the symptoms of right ventricular (RV) failure..

Chest radiography.

Radiographic examination of the chest in patients with pulmonary hypertension shows enlargement of the main pulmonary artery and its major branches, with marked tapering of peripheral arteries. The right ventricle and atrium may also be enlarged. Dilation of the right ventricle gives the heart a globular appearance, but right ventricular hypertrophy or dilation is not easily discernible on a plain chest radiograph. Encroachment of the retrosternal air space on the lateral film may be a helpful sign to confirm that the enlarged silhouette is a result of right ventricular dilation. The lung fields should be clear, and often appear darkened from the relative oligemia caused by a low cardiac output.

Electrocardiography .

The electrocardiogram in patients with PAH usually exhibits right atrial and right ventricular enlargement. T wave inversion, representing the

repolarization abnormalities associated with right ventricular hypertrophy (RVH) are usually seen in the anterior precordial leads and may be mistaken for anteroseptal ischemia.

Echocardiography .

Echocardiography usually demonstrates enlargement of the right atrium and ventricle, normal or small left ventricular dimensions, and a thickened interventri-cular septumAbnormal septal motion as a result of the right ventricular pressure overload is characteristic..

Doppler echocardiographic estimates of right ventricular systolic pressures can be obtained by measuring the velocity of the tricuspid regurgitant jet and using the Bernoulli formula . Although Doppler measurements correlate with right ventricular systolic pressure, they are relatively imprecise (±20 mm Hg) and are not a substitute for catheterization if a correct measurement of pulmonary pressure is needed. Doppler echocardiography has also demonstrated that left ventricular diastolic dysfunction develops from the pulmonary hypertensive state, with marked dependence on atrial contraction for ventricular filling.

Radionuclide Ventriculography.

Radionuclide ventriculography can provide useful information regarding right ventricular function, provided that adequate separation of the cardiac chambers can be accomplished. Because radioactive counts are proportional to volume, variations in the geometric configuration of the ventricles are less important. Although pulmonary artery pressure cannot be estimated with this technique, there is an inverse relationship between pulmonary artery pressure and right ventricular ejection fraction.

Pulmonary Function Tests.

A significant obstructive pattern is not characteristic and suggests obstructive airways disease. In patients with PAH, the diffusing capacity for carbon monoxide (DLCO) is reduced to approximately 60 to 80 percent of predicted; there is no clear correlation between severity of the disease and the DLCO. The presence of arterial hypoxemia is caused by ventilation-perfusion mismatch and/or reduced mixed venous oxygen saturations resulting from low cardiac output. .

Approximately 20 percent of patients with systemic sclerosis have an isolated reduction in DLCO, which, when severe (less than 55 percent of predicted), can be associated with the development of PAH. In patients with limited systemic sclerosis, a fall in DLCO in the presence of normal lung volumes often precedes the onset of PAH.

Lung Scintigraphy.

A perfusion lung scan is an important test in making the correct diagnosis of pulmonary hypertension. Patients with PAH may reveal a relatively normal perfusion pattern or diffuse, patchy, perfusion abnormalities. A perfusion lung scan will reliably distinguish patients with PAH from those who have pulmonary hypertension secondary to chronic pulmonary thromboembolism.

Computed Tomography

Spiral chest CT scans have been used successfully in diagnosing chronic thromboembolic pulmonary hypertension. High-resolution CT is the best test by which to diagnose interstitial lung disease. It has a high degree of specificity, but its sensitivity is low. However, patients with PAH without coexisting lung disease should have normal lung parenchyma. Thus,

although CT tends to underrepresent the extent of the disease, the presence of any interstitial abnormality would suggest that interstitial lung disease is underlying the pulmonary hypertension. A high-resolution CT scan of the chest is also an accurate means of detecting emphysema.

Pulmonary Angiography.

Pulmonary angiography establishes the correct diagnosis in patients with pulmonary hypertension in whom a perfusion lung scan suggests segmental or lobar defects. Although pulmonary angiography carries an increased risk in patients with pulmonary hypertension, it can be performed safely if adequate precautions are taken. Maintenance of adequate oxygenation by the administration of supplemental oxygen and the avoidance of vasovagal reactions, and rapid treatment of those that occur with intravenous atropine, should reduce the associated risk in this patient group. Continuous arterial pressure monitoring is advised, and nonionic contrast agents appear to be better tolerated.

CLUES FOR INTERPRETATION OF DIAGNOSTIC TESTS FOR PULMONARY HYPERTENSION

Test	Notable Findings
Chest x-ray	Enlargement of central pulmonary arteries reflects level of PA pressure and duration.
Electrocardiography	Right axis deviation and precordial T wave abnormalities are early signs.
Pulmonary function tests	Elevated pulmonary artery pressure causes restrictive physiology.
Perfusion lung scan	Nonsegmental perfusion abnormalities can occur from severe pulmonary vascular disease.
Chest computed tomography scan	Minor interstitial changes may reflect diffuse disease; mosaic perfusion pattern indicates thromboembolism and/or left heart failure.
Echocardiography	Right ventricular enlargement will parallel the severity of the pulmonary hypertension.
Contrast echocardiography	Minor right to left shunting rarely produces hypoxemia.
Doppler echocardiography	This is too unreliable for following serial measurements to monitor therapy.
Exercise testing	This is very helpful to assess the efficacy of therapy. Severe exercise-induced hypoxemia should cause consideration of a right-to-left shunt.

CARDIAC CATHETERIZATION.

In addition to confirming the diagnosis and allowing the exclusion of other causes, cardiac catheterization also establishes the severity of disease and allows an assessment of prognosis. By definition, patients with PAH should have a low or normal pulmonary capillary wedge pressure. Because this is a critical measurement in distinguishing a patient with PAH from one with pulmonary venous hypertension, several quality measures must be established in the catheterization laboratory to ensure that correct values are obtained.

HEMODYNAMIC ASSESSMENT OF VASODILATORS IN PULMONARY HYPERTENSION

Parameter Measured	Desired Acute Changes	Comments
Mean pulmonary artery pressure (PAP)	>10-mm Hg decrease; ideally, mean PAP below 30 mm Hg	Must not be associated significant fall in systemic blood pressure
Pulmonary vascular resistance (PVR)	>33% decrease; ideally, PVR below 6 units	Cardiac output unchanged or increased
Pulmonary capillary wedge pressure	No change	Increase in wedge pressure suggests pulmonary venoocclusive disease or coexisting left ventricular dysfunction
Cardiac output	Increase	Increase should be from increased stroke volume rather than increased heart rate
Heart rate	No significant change	Chronic increased heart rate will result in RV failure; watch for bradycardia if using high doses of diltiazem
Systemic arterial oxygen saturation	Increase if reduced on room air, little change if normal	Decrease in systemic arterial oxygen saturation suggests lung disease or right-to-left shunt; prohibits chronic use
Pulmonary artery (mixed venous) oxygen saturation	Increase	Should parallel increase in cardiac output and improved tissue oxygenation

HISTOPATHOLOGICAL CLASSIFICATION OF HYPERTENSIVE PULMONARY VASCULAR DISEASE

Classification Arteriopathy	Characteristic Histopathological Features
Isolated medial hypertrophy[*]	Medial hypertrophy: increase of medial muscle in muscular arteries, muscularization of nonmuscularized arterioles; no appreciable intimal or luminal obstructive lesions; no plexiform lesions
Plexogenic pulmonary	Plexiform and dilation lesions; medial hypertrophy; eccentric or concentric laminar and nonlaminar arteriopathy, intimal thickening; fibrinoid necrosis, arteritis, and thrombotic lesions
Thrombotic pulmonary	Thrombi (fresh, organizing, or organized and colander lesions); eccentric and concentric nonlaminar arteriopathy, intimal thickening, varying degrees of medial hypertrophy; no plexiform lesions
Isolated pulmonary arteritis	Active or healed arteritis, limited to pulmonary arteries; varying degrees of medial hypertrophy, intimal fibrosis, and thrombotic lesions; no plexiform lesions; no systemic arteritis
Venopathy	
Pulmonary venoocclusive disease	Eccentric intimal fibrosis and recanalized thrombi within diseased pulmonary veins and venules; arterialized veins, capillary congestion, alveolar edema and siderophages, dilated lymphatics, pleural and septal edema, and arterial medial hypertrophy; intimal thickening and thrombotic lesions

THROMBOTIC PULMONARY ARTERIOPATHY.

The other major pattern of vascular changes in PAH is that of a thrombotic pulmonary arteriopathy. Typical features include medial hypertrophy of the arteries and arterioles, with both eccentric and concentric nonlaminar intimal fibrosis. The presence of colander lesions, which represent recanalized thrombi, is also typical. These lesions are believed to arise as a result of primary in situ thrombosis of the small vascular arteries and not from recurrent pulmonary embolism.

Many patients will have characteristics of both patterns of arteriopathy of varying degrees. This would suggest that the vascular changes from PAH occur across a spectrum, and are likely influenced by genetic and environmental factors.

DYSFUNCTIONAL ENDOTHELIUM.

The dysfunctional pulmonary hypertensive endothelial cell phenotype is characterized by uncontrolled proliferation, increased production of vasoconstrictor mediators such as endothelin, expression of 5-lipooxygenase, and decreased synthesis of prostacyclin..

Reduced expression of the endothelial isoform of NO synthase has been demonstrated in the pulmonary vasculature and correlates inversely with the extent and severity of morphological lesions.

A striking feature of the pulmonary vasculature in patients with IPAH is intimal proliferation and, in some vessels, it causes virtually complete vascular occlusion. Several growth factors have been implicated in the development of this type of vascular pathology, including basic fibroblast growth factor from the endothelium..

ION CHANNELS.

Potassium channels are found throughout the pulmonary vascular bed. They consist of voltage-dependent and calcium-dependent potassium channels . The role of these channels has been studied primarily in the presence of acute hypoxia in animals. It is believed that potassium channels modulate adult pulmonary vascular tone. It is probable that calcium channels also serve a regulatory role in modulating vascular tone, particularly the L-type calcium channel. Inhibition of the voltage-regulated potassium channel by hypoxia or drugs can produce vasoconstriction and has been described in pulmonary artery smooth muscle cells harvested from patients with IPAH...

SEROTONIN.

Elevated plasma levels of serotonin and reduced platelet serotonin concentration have been described in IPAH patients. Mutations in the serotonin transporter and 5-hydroxytryptamine 2B ($5\text{-}HT_{2B}$) receptor have now been reported in patients with IPAH.

ELASTOLYTIC ENZYMES.

High elastin turnover and neosynthesis of elastin have been attributed to degradation of elastin from the increased activity of serine elastase.. Enzymes released from precursor or mature smooth muscle cells activate growth factors normally stored in the extracellular matrix, such as basic fibroblast growth factor and TGF-b, which are known to induce smooth muscle cell hypertrophy and proliferation and increase connective tissue protein synthesis. In muscular arteries, release of growth factors would result in hypertrophy of the vessel wall.

OTHER VASCULAR PROTEINS.

Increased plasma levels of adrenomedullin occur in PAH and hypoxic pulmonary hypertension.. Vasoactive intestinal peptide decreases pulmonary artery pressure and pulmonary vascular resistance and inhibits platelet

activation and smooth muscle cell proliferation. Increased levels have been reported in PAH

FAMILIAL PULMONARY ARTERIAL HYPERTENSION.

Idiopathic PAH has been diagnosed in families worldwide. The prevalence of familial PAH (FPAH) is uncertain, but it occurs in at least 6 percent of cases, and the incidence is likely higher. The age of onset is variable and the low penetrance of the gene confers only about a 20 percent likelihood of development of the disease. Many individuals in families with PAH inherit the gene and have progeny in whom PAH never develops.

Bone Morphogenetic Protein Receptor Type 2 Gene.

Using linkage analysis, the locus designated PPH-1 on chromosome 2q33 led to the discovery of the *PPH-1* gene. *PPH-1* is the Human Genome Organization–approved designation DGB:1381541. The bone morphogenetic protein receptor type 2 gene (*BMPR-2*) codes for a receptor member of the TGF-b family . *BMPR-2* modulates vascular cell growth by activating the intracellular pathways of Smad and LIM kinase. . Recent data have supported the hypothesis that the predominant molecular mechanism underlying PAH is haploinsufficiency for *BMPR-2*.

Other Genetic Factors.

There is overexpression of serotonin transporter (5-hydroxytryptamine transporter, 5-HTT) in pulmonary arteries and platelets from all the patients with PAH.

Defects in a common vascular signaling pathway involving angiopoetin-1 have also been described. Increased signaling has been noted which causes phosphorylation of the endothelial-specific TIE-2 receptor. This reduces the level of the BMPR-1A receptor which is necessary for normal BMPR-2 signaling.

RIGHT VENTRICULAR FUNCTION

Right ventricular failure from pulmonary hypertension is a result of chronic pressure overload and associated volume overload, with the development of tricuspid regurgitation.. The mechanism of right ventricular failure in patients with pulmonary hypertension is complex. The chronic pressure overload that induces right ventricular hypertrophy and reduced contractility has been shown to cause a reduction in coronary blood flow to the right ventricular myocardium, which can produce right ventricular ischemia, both acutely and chronically. Such right ventricular dysfunction

appears to be a result of a reduction in right ventricular coronary artery driving pressure.

LEFT VENTRICULAR FUNCTION.

On occasion, patients with pulmonary hypertension have a reduced left ventricular ejection fraction and even regional wall motion abnormalities of the left ventricle. In the past, these findings had been attributed to mechanisms related to interventricular dependence, which suggests that in some way a dysfunctional right ventricle can lead to a dysfunctional left ventricle. Clearly, the shared interventricular septum can affect the function of both ventricles. .

MANAGEMENT

LIFESTYLE CHANGES

Graded exercise activities, such as bike riding or swimming, in which patients can gradually increase their workload and easily limit the extent of their work, are thought to be safer than isometric activities. Isometric activities such as lifting weights or stair climbing can be associated with syncopal events and should be limited or avoided.

PREGNANCY ISSUES

Surgical sterilization should be given strong consideration by women with IPAH or their husbands, and pregnancy should be strongly discouraged.

MEDICAL THERAPIES

Medical therapies have been developed that are targeted at reversing the severity of pulmonary hypertension via many different pathways.

DIGOXIN.

Digoxin helps prevent the reduction in contractility of the right ventricle. Clinically, it has been shown that digoxin can exert a favorable hemodynamic effect when given acutely to patients with right ventricular failure from pulmonary hypertension..

DIURETICS

These drugs appear to be of marked benefit in symptom relief of patients with IPAH. Their traditional role has been limited to patients manifesting right ventricular failure and systemic venous congestion. However, patients with advanced IPAH can have increased left ventricular filling pressures that contribute to the symptoms of dyspnea and orthopnea, which can be relieved with diuretics. Diuretics may also serve to reduce

right ventricular wall stress in patients with concomitant tricuspid regurgitation and volume overload. Patients with severe venous congestion may require high doses of loop diuretics or the use of combined diuretics. .

Spironolactone has been demonstrated to enhance the beneficial effect of ACE inhibition on mortality in patients with congestive heart failure. Given the similarities between left and right heart failure on activation of the renin-angiotensin-aldosterone system, it seems reasonable to use aldosterone antagonists in patients with pulmonary hypertension.

SUPPLEMENTAL OXYGEN.

Hypoxic pulmonary vasoconstriction can contribute to pulmonary vascular disease in patients with alveolar hypoxia from parenchymal lung disease. Supplemental low-flow oxygen alleviates arterial hypoxemia and attenuates the pulmonary hypertension in patients with these disorders. .

ANTICOAGULANTS.

Oral anticoagulant therapy is widely recommended for patients with PAH.Patients who received warfarin had improved survival over those who did not.. The current recommendation is to use warfarin in relatively low

doses, as has been recommended for prophylaxis of venous thromboembolism, with the international normalized ratio (INR) maintained at 2.0 to 3.0 times that of controls.

VASODILATOR THERAPY

CALCIUM CHANNEL BLOCKERS.

Of the vasodilators prescribed for patients with IPAH, calcium channel blockers appear to have the widest use.. It has been reported that 10 to 20 percent of patients with IPAH who are challenged with very high doses of calcium channel blockers may manifest a dramatic reduction in pulmonary artery pressure and pulmonary vascular resistance, It appears essential that high doses (e.g., amlodipine, 20 to 30 mg/day; nifedipine, 180 to 240 mg/day; diltiazem, 720 to 960 mg/day) be used to realize full benefit.

PROSTACYCLINS.

Prostacyclins have been found to be effective in the therapy of pulmonary arterial hypertension. Continuous intravenous infusion of *epoprostenol* has been shown in randomized clinical trials to improve quality of life and symptoms related to IPAH.. Patients may have a reduction in pulmonary vascular resistance of more than 50 percent, even if no acute hemodynamic effects are noted.

Side effects related to epoprostenol include flushing, headache, nausea, diarrhea, and a unique type of jaw discomfort that occurs with eating. In most patients, these symptoms are minimal and well tolerated. Chronic foot pain and a poorly defined gastropathy with prolonged use develop in some patients. .*Treprostinil* is a stable prostacyclin analogue that has pharmacological actions similar to those of epoprostenol, .*Iloprost*, an analogue of prostacyclin, has been approved for use via inhalation. eraprost improved exercise capacity and symptoms over a 12-week period but had no significant effect on cardiopulmonary hemodynamics or functional class. .

ENDOTHELIN RECEPTOR BLOCKERS.

Bosentan is a nonselective endothelin receptor blocker that is approved as a treatment of pulmonary arterial hypertension. Bosentan showed a significant improvement in 6-minute walk distance after 16 weeks as compared with placebo. The approved dosage of bosentan is 125 mg twice daily.

PHOSPHODIESTERASE TYPE 5 INHIBITORS.

Sildenafil is a phosphodiesterase type 5 (PDE5) inhibitor produces pulmonary vasodilation by promoting an enhanced and sustained level of

cGMP, an identical effect to that of inhaled NO. The recommended dosage is 20 mg three times daily, but dosages as high as 80 mg three times daily have been used safely.

Invasive Techniques

ATRIAL SEPTOSTOMY.

The rationale for the creation of an atrial septostomy in patients with PAH is based on experimental and clinical observations suggesting that an intraatrial defect allowing right-to-left shunting in the setting of severe pulmonary hypertension might be of benefit.

The mechanisms responsible for the beneficial effects of atrial septostomy remain unclear. Possibilities include increased oxygen delivery at rest and/or with exercise, reduced right ventricular end-diastolic pressure or wall stress, improvement in right ventricular function as by the Frank-Starling curve, or relief of ischemia.

HEART-LUNG AND LUNG TRANSPLANTATION.

Transplantation should be reserved for patients with pulmonary hypertension who have progressed in spite of optimal medical management. It is generally accepted that patients should be considered for transplantation

when they have WHO functional class III or IV disease in spite of therapy with a parenteral prostacyclin.

Pulmonary Arterial Hypertension Associated with Congenital Heart Disease

Pulmonary hypertension can develop in adults with an atrial septal defect,increased pulmonary blood flow from hyperthyroidism and beriberi, patients with pretricuspid shunts, such as atrial septal defect or anomalous pulmonary venous drainage.

EISENMENGER SYNDROME.

This refers to any anomalous circulatory communication that leads to obliterative pulmonary vascular disease, including pretricuspid and posttricuspid shunts The long-term prognosis of patients with Eisenmenger syndrome appears to be better than that of patients with other conditions associated with pulmonary hypertension..

Pulmonary Arterial Hypertension Associated with Connective Tissue Diseases

Scleroderma, including the CREST syndrome, is the most common cause of pulmonary hypertension in connective tissue disease states. Scleroderma is associated with pulmonary hypertension in as many as one

third of patients and with CREST syndrome in as many as 50 percent.. Patients with systemic lupus erythematosus also have pulmonary hypertension, although less commonly than patients with scleroderma. Mixed connective tissue disease is a less common form of connective tissue disease, but pulmonary hypertension may occur in as many as two thirds of these patients. Pulmonary hypertension has also been described in patients with polymyositis, dermatomyositis, and rheumatoid arthritis.

Pulmonary Arterial Hypertension Associated with Portal Hypertension

Pulmonary abnormalities have been commonly associated with the development of hepatic cirrhosis and portal hypertension and include hypoxemia and intrapulmonary shunting, portal-pulmonary shunting, impaired hypoxic pulmonary vasoconstriction, and pulmonary hypertension.

Pulmonary Arterial Hypertension Associated with Human Immunodeficiency Virus Infection

Although well documented, it remains unclear how HIV infection results in an increased incidence of PAH in HIV-infected patients. A direct pathogenic role of HIV seems unlikely, inasmuch as no viral constituents have been detected in the vascular endothelium of these patients. On the other hand, reports of pulmonary arteriopathy with intimal proliferation in

monkeys experimentally infected with the simian immunodeficiency virus and in a murine model of acquired immunodeficiency syndrome have suggested a pathogenetic link between infection with an immunodeficiency virus and the development of PAH..

Pulmonary Arterial Hypertension Related to Anorexigens

Aminorex, fenfluramine have been demonstrated in the development of PAH

Pulmonary Hypertension Related to Sickle Cell Disease

Cardiopulmonary complications are common in sickle cell disease. The cause of pulmonary hypertension, which has been reported in 20 to 32 percent of sickle cell disease patients, is multifactorial, with contributing factors including hemolysis, impaired nitric oxide bioavailability, chronic hypoxemia, high cardiac output, thromboembolism, and parenchymal and vascular injury caused by sequestration of sickle erythrocytes, chronic liver disease, and asplenia.

Persistent Pulmonary Hypertension of the Newborn

Three forms of persistent pulmonary hypertension of the newborn have been described. In the hypertrophic type, the muscular tissue of the

pulmonary arteries is hypertrophied and extends peripherally to the acini. In the hypoplastic type, the lungs, including the pulmonary arteries, are underdeveloped, usually as the result of a congenital diaphragmatic hernia or prolonged leakage of amniotic fluid. The cross-sectional area of the pulmonary vascular bed is inadequate for normal neonatal pulmonary blood flow. In the reactive type, lung histology is presumably normal but vasoconstriction causes pulmonary hypertension. High levels of vasoconstrictive mediators such as thromboxane, norepinephrine, and leukotrienes may be responsible and may result from streptococcal infection or acute asphyxia at birth.

Pulmonary Venoocclusive Disease

Pulmonary venoocclusive disease is a rare form of PAH.[60] The histopathological diagnosis is based on the presence of obstructive eccentric fibrous intimal pads in the pulmonary veins and venules.

Pulmonary Capillary Hemangiomatosis

Pulmonary capillary hemangiomatosis was first described in 1978 as a very rare cause of pulmonary hypertension.

Pulmonary Venous Hypertension

Pathophysiology

Increased resistance to pulmonary venous drainage is a mechanism common to several conditions of diverse causes in which pulmonary hypertension occurs. Altered resistance to pulmonary venous drainage may be the result of diseases affecting the left ventricle or pericardium or mitral or aortic valves, or of rare entities such as cor triatriatum and left atrial myxoma.

PULMONARY ARTERIAL VASOCONSTRICTION.

Considerable variability in pulmonary arterial vasoconstriction occurs in response to pulmonary venous hypertension. Marked reactive pulmonary hypertension with pulmonary artery systolic pressures in excess of 80 mm Hg occurs in somewhat less than one third of patients whose pulmonary venous pressures are elevated more than 25 mm Hg. The fact that severe reactive pulmonary hypertension develops in fewer than one third of patients with severe mitral stenosis suggests a broad spectrum of pulmonary vascular reactiv-ity to chronic increases in pulmonary venous pressure. .

Sarcoidosis

Pulmonary hypertension is most commonly the result of chronic severe fibrocystic sarcoidosis. Patients have chronic progressive dyspnea with effort, a chest radiograph demonstrating severe diffuse interstitial fibrotic lung disease, and pulmonary function test results that reflect severe restrictive physiology and hypoxemia. In these cases, the resulting pulmonary hypertension is usually mild to moderate and typical of patients presenting with restrictive lung disease of any cause.

Pulmonary Arterial Hypertension Associated with Disorders of the Respiratory System

Diseases of the lung parenchyma are a common cause of pulmonary hypertension. The pathogenic mechanisms that can lead to pulmonary hypertension in this setting are shown in Table .

Potential Pathogenic Mechanisms Leading to Pulmonary Arterial Hypertension and Cor Pulmonale

Mechanisms	Example(s)
Primary	
Anatomical decrease in cross-sectional area (vessel destruction; encroachment on lumen by hypertrophy) of the pulmonary resistance vessels	Interstitial fibrosis and granuloma
Vasoconstriction of pulmonary resistance vessels	Hypoxia and acidosis
Contributory	
Large increments in pulmonary blood flow	Exercise
Increased pressures on the left side of the heart and pulmonary veins	Left ventricular failure or pulmonary venoocclusive disease
Increased viscosity of the blood	Secondary polycythemia or chronic hypoxia
Unproved	
Compression of pulmonary resistance vessels by raised alveolar pressures in their vicinity	Asthmatic bronchitis
Bronchial arterial-pulmonary arterial anastomoses	Expanded bronchial circulation

PULMONARY HYPERTENSION IN COPD.

Most commonly, pulmonary hypertension in COPD patients has multiple causative factors, including pulmonary vasoconstriction caused by alveolar hypoxia, acidemia, and hypercarbia, the compression of pulmonary vessels by the high lung volume, the loss of small vessels in the vascular bed in regions of the emphysema and lung destruction, and increased cardiac output and blood viscosity from polycythemia secondary to hypoxia.. Of these, hypoxia is the most important factor and is associated with pathological changes that occur characteristically in the peripheral pulmonary arterial bed.

Key Indicators for Considering a Diagnosis of Chronic Obstructive Pulmonary Disease (COPD)[*]

Stage	Characteristics
Chronic cough	Present intermittently or every day
	Often present throughout the day; seldom only nocturnal
Chronic sputum production	Any pattern of chronic sputum production may indicate COPD
Dyspnea that is	Progressive (worsens over time)
	Persistent (present every day)
	Described by the patients as “increased effort to breathe,” “heaviness,” “air hunger,” or “gasping”
	Worse on exercise
	Worse during respiratory infections

Interstitial Lung Diseases

Interstitial lung diseases represent various conditions that involve the alveolar walls, perialveolar tissue, and other contiguous supporting structures. Pulmonary hypertension occurs in patients with interstitial lung diseases and is often associated with obliteration of the pulmonary vascular bed by lung destruction and fibrosis. .

ADULT CYSTIC FIBROSIS.

Cystic fibrosis is the most common lethal genetic disease in whites and occurs in approximately 1 of every 2000 live births. As the disease progresses, patients develop disabling lung disease and eventually respiratory failure, pulmonary hypertension, and cor pulmonale..

Sleep-Disordered Breathing and Pulmonary Hypertension

Observational studies have demonstrated a wide variation in the incidence of pulmonary hypertension as a complication of sleep apnea, with a wide range of severity. The diagnosis of pulmonary hypertension in obstructive sleep apnea patients is also clouded by the coexistence of systemic hypertension, obesity, and diastolic dysfunction..

Alveolar Hypoventilation Disorders

Alveolar hypoventilation disorders are characterized by hypoxemia and mechanical disorders of the ventila-tory system which, in concert, may cause pulmonary hypertension.

CHEST WALL DISORDERS.

Thoracovertebral deformities like idiopathic kyphoscoliosis, spinal tuberculosis, congenital spinal developmental abnormalities, spinal cord injury and other childhood myelopathies, ankylosing spondylitis, or other congenital and acquired muscular skeletal conditions, such as pectus excavatum.

NEUROMUSCULAR DISEASE.

Disorders like myopathic infiltrating diseases or muscular dystrophy , amyotrophic lateral sclerosis, myasthenia gravis, poliomyelitis, and Guillain-Barré syndromecause pulmonary hyprertension..

DIAPHRAGMATIC PARALYSIS.

Bilateral diaphragmatic paralysis is an uncommon and rarely recognized cause of pulmonary hypertension. Diaphragmatic paralysis is a result of phrenic nerve injury, which can be traumatic or secondary to an underlying motor neuron disease. It may occur after cardiac surgery, as a

manifestation of Lyme disease, after radiation therapy, or as a manifestation of other neurological disorders..

Pulmonary Hypertension Caused by Chronic Thrombotic or Embolic Obstruction of the Pulmonary Arteriees

Chronic thromboembolic pulmonary hypertension is an underdiagnosed disorder, and the true prevalence is still unclear. Pulmonary embolism, either as a single episode or as recurrent events, is thought to be the initiating process, followed by progressive vascular remodeling.

Pulmonary Hypertension Caused by Disorders Directly Affecting the Pulmonary Vasculature

Schistosomiasis

Although schistosomiasis is extremely rare in North America, hundreds of millions of people are affected worldwide, particularly in developing countries. The development of pulmonary hypertension almost always occurs in the setting of hepatosplenic disease and portal hypertension.

MATERIALS AND METHODS

This study was performed in the Department of Cardiology, Government General Hospital, Chennai, during the year 2006 – 2009,after approval from the Institutional Ethical Committee, Madras Medical College, Chennai – 3. (Ref – K . Dis.No.002909 / P & D3 /Ethics /Dean /GGH /09)

STUDY INDICATION :

- To differentiate primary PHT from secondary PHT with the use of MPI [Myocardial Performance Index] [TEI INDEX]
- To study the effects of primary PHT and secondary PHT on right ventricular function.
- To study the effects of primary PHT and secondary PHT on left ventricular function.
- To estimate the mean pulmonary artery pressure (mPAP) in primary PHT and secondary PHT.
- To estimate the pulmonary capillary wedge pressure (PCWP) in primary PHT and secondary PHT.

STUDY GROUP SELECTION

STUDY GROUP : CONSISTED 60 PERSONS.

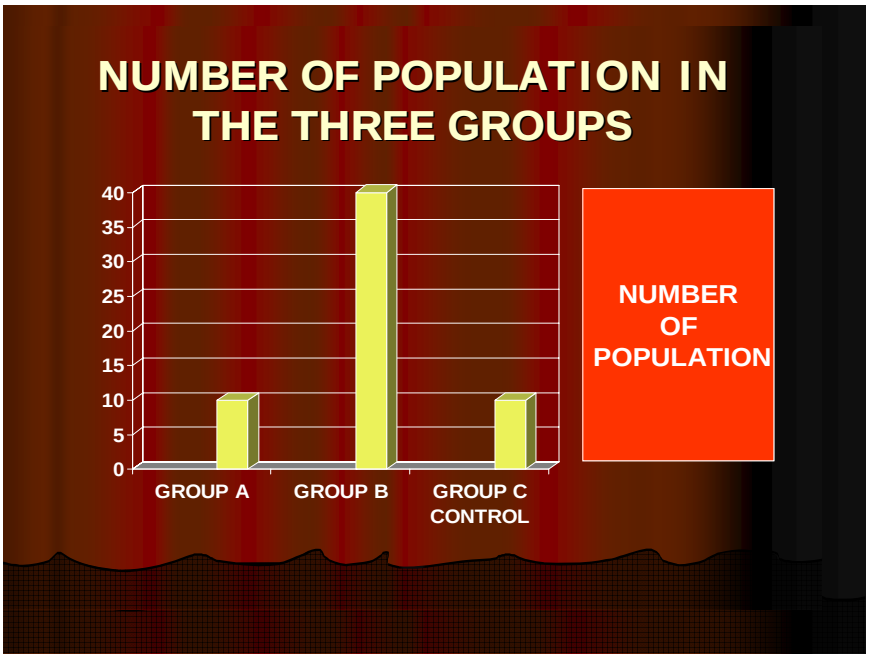
GROUP A : 10 CASES OF PRIMARY PULMONARY HYPERTENSION

GROUP B : 40 CASES OF SECONDARY PULMONARY HYPERTENSION

GROUP C : 10 NORMAL PERSONS [CONTROL GROUP]

GROUP B

10 Cases ASD with Reversal
10 Cases VSD with Reversal
10 Cases PDA with Reversal
5 Cases Pulmonary Embolism
5 Cases COPD

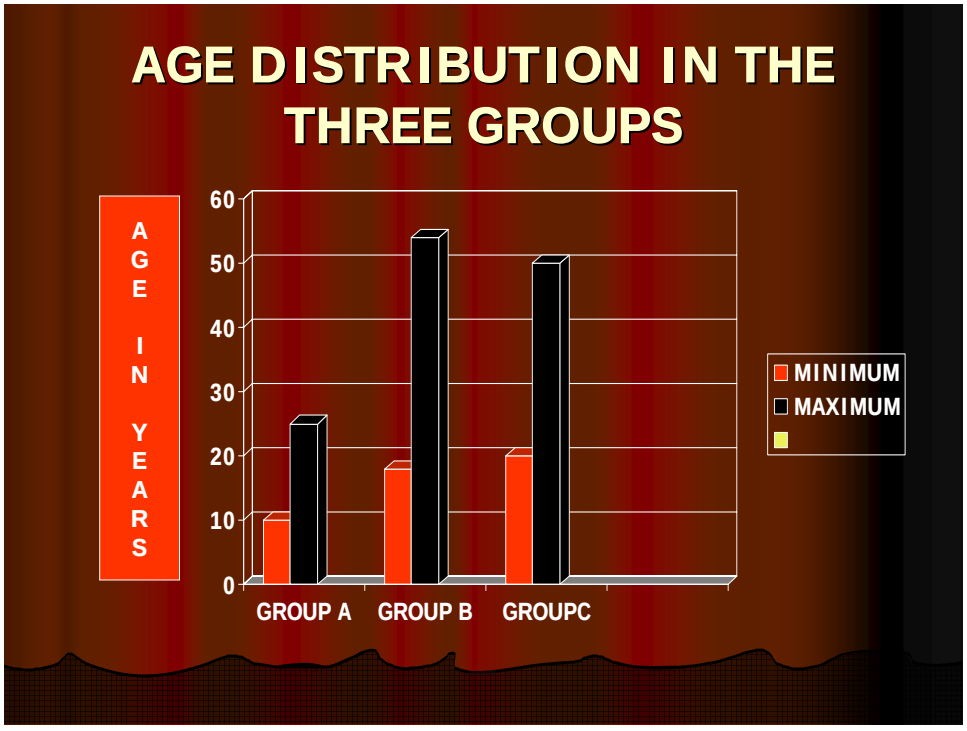


STUDY DESIGN :

CASE CONTROL STUDY [OBSERVATIONAL STUDY]

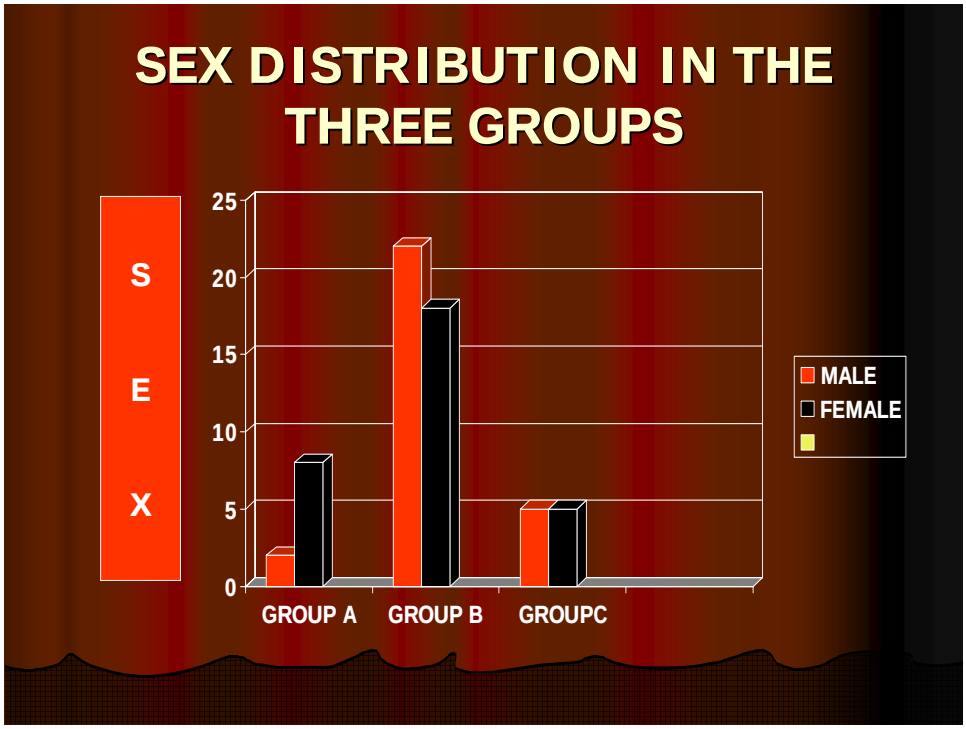
AGE DISTRIBUTION

	AGE IN YEARS
GROUP A	10 – 25
GROUP B	18 – 54
GROUP C	20 – 50



SEX DISTRIBUTION

	MALES	FEMALES
GROUP A	2	8
GROUP B	22	18
GROUP C	5	5



SMOKING HABITUS

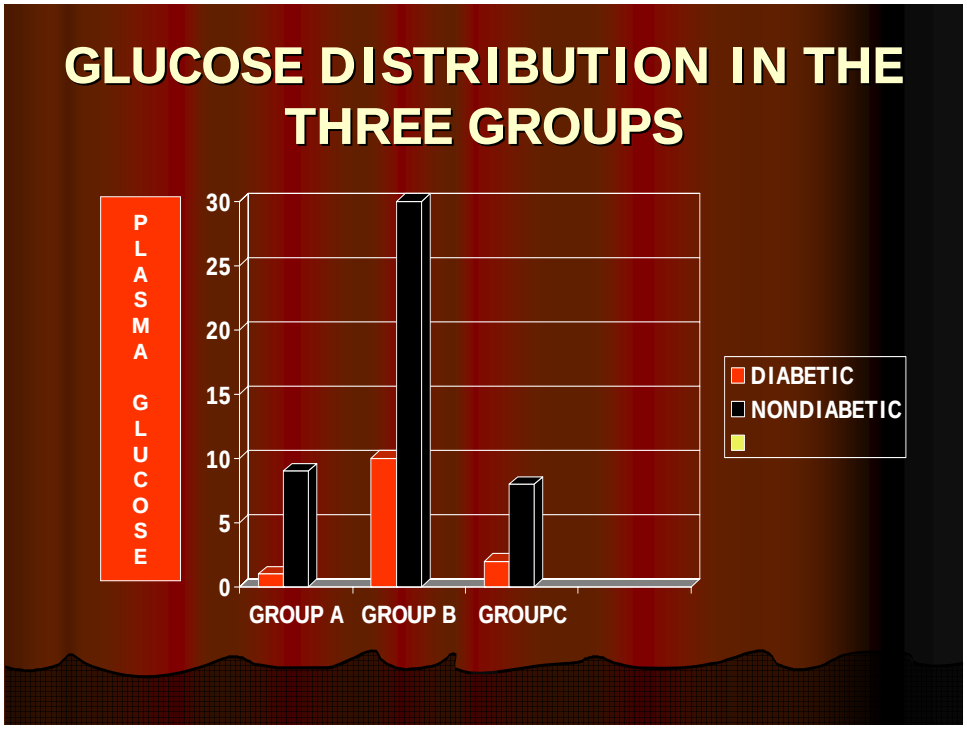
	SMOKER	NONSMOKER
GROUP A	2	8
GROUP B	18	22
GROUP C	2	8

ALCOHOL ABUSE HABITUS

	ALCOHOLIC	NONALCOHOLIC
GROUP A	1	9
GROUP B	10	30
GROUP C	1	9

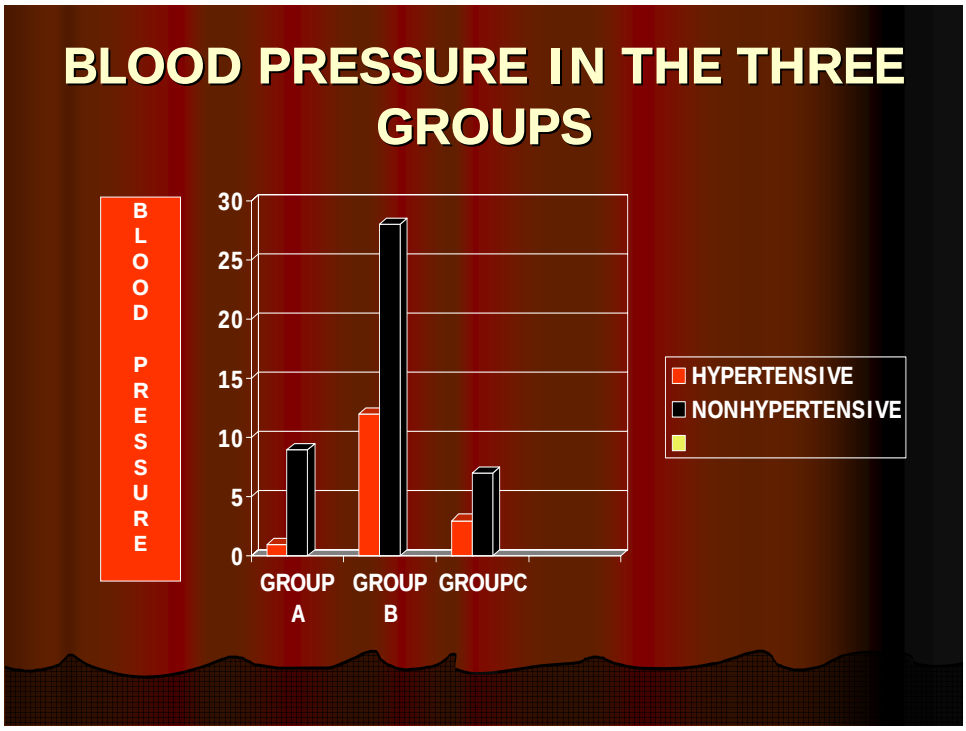
BLOOD GLUCOSE DISTRIBUTION IN THE THREE GROUPS

	DIABETIC	NONDIABETIC
GROUP A	1	9
GROUP B	10	30
GROUP C	2	8



BLOOD PRESSURE DISTRIBUTION IN THE THREE GROUPS

	HYPERTENSIVE	NONHYPERTENSIVE
GROUP A	1	9
GROUP B	12	28
GROUP C	3	7



The following parameters were done to differentiate primary pulmonary hypertension from secondary pulmonary hypertension.

1) **RV MPI**
2) **LV MPI**
3) **MITAL E VELOCITY [m/sec]**
4) **MITRAL INFLOW PROPAGATION VELOCITY[cm/sec] Vp**
5) **PCWP [mmHg]**
6) **RV dP/dT [mmHg/sec]**
7) **MPAP [mmHg/sec]**
8) **LV dP/dt [mmHg/sec]**
9) **LVOT Acceleration (m/sec^2)**

- Echo Machine Philips IE33 was used for Echocardiographic Parameters.
- Philips Integris angiographic machine was used for Angiographic Parameters.

RESULTS AND DATA ANALYSIS

RV MPI

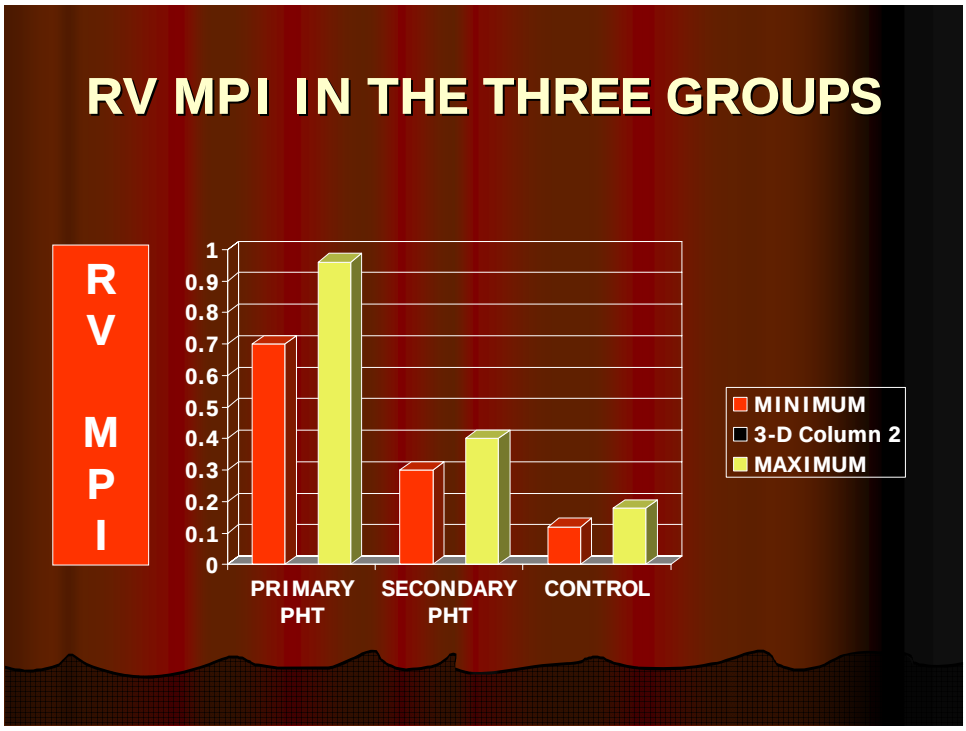
Normally RV MPI does not exceed 0.2.

In GROUP A, RV MPI always exceeds 0.7.

In GROUP B, RV MPI is in the range of 0.3 to 0.4.

In GROUP C, RV MPI is kept in the normal range.

	RV MPI	MEAN	P Value
GROUP A	0.7 – 0.96	0.8	< 0.01
GROUP B	0.3 – 0.4	0.36	< 0.02
GROUP C	0.12 – 0.18	0.15	<0.01



LV MPI

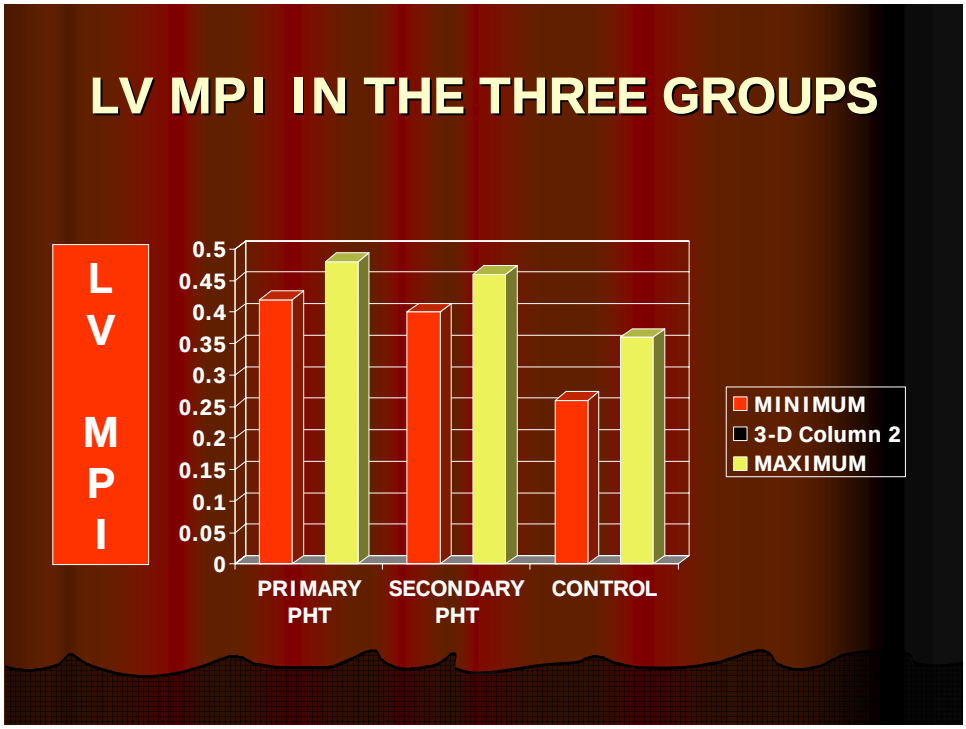
Normally LV MPI does not exceed 0.4.

In GROUP A, LV MPI is in the range of 0.42 – 0.48.

In GROUP B, LV MPI is in the range of 0.4 – 0.46.

In GROUP C, LV MPI is kept in the normal range

	RV MPI	MEAN	P Value
GROUP A	0.42 – 0.48	0.45	< 0.01
GROUP B	0.4 – 0.46	0.43	< 0.02
GROUP C	0.26 – 0.36	0.32	< 0.01



MITRAL E VELOCITY

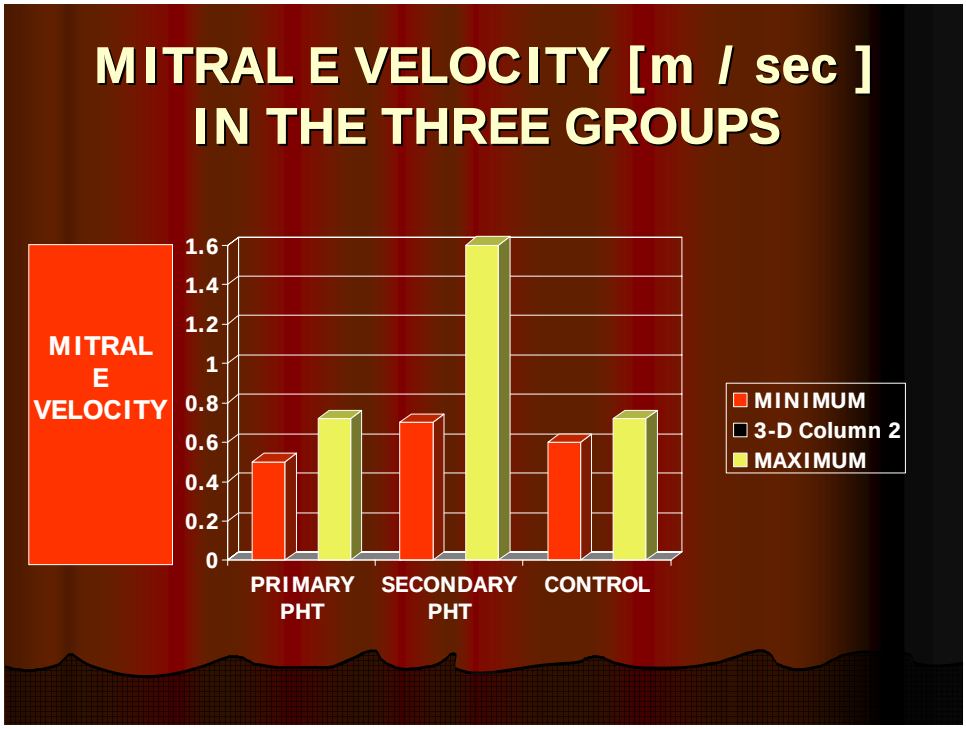
Normally, E VELOCITY is in the range of 0.6 – 0.9 m / sec.

In Group A, E VELOCITY is in the range of 0.52 – 0.72 m /sec.

In Group B, E VELOCITY is in the range of 0.7 – 1.6 m /sec.

In Group C, E VELOCITY is kept in the normal range

	MITRAL E VELOCITY (m /sec)	MEAN	P Value
GROUP A	0.52 – 0.72	0.62	< 0.01
GROUP B	0.7 – 1.6	1.2	< 0.02
GROUP C	0.6 – 0.7	0.65	< 0.01



MITRAL INFLOW PROPAGATION VELOCITY (cm / sec): Vp

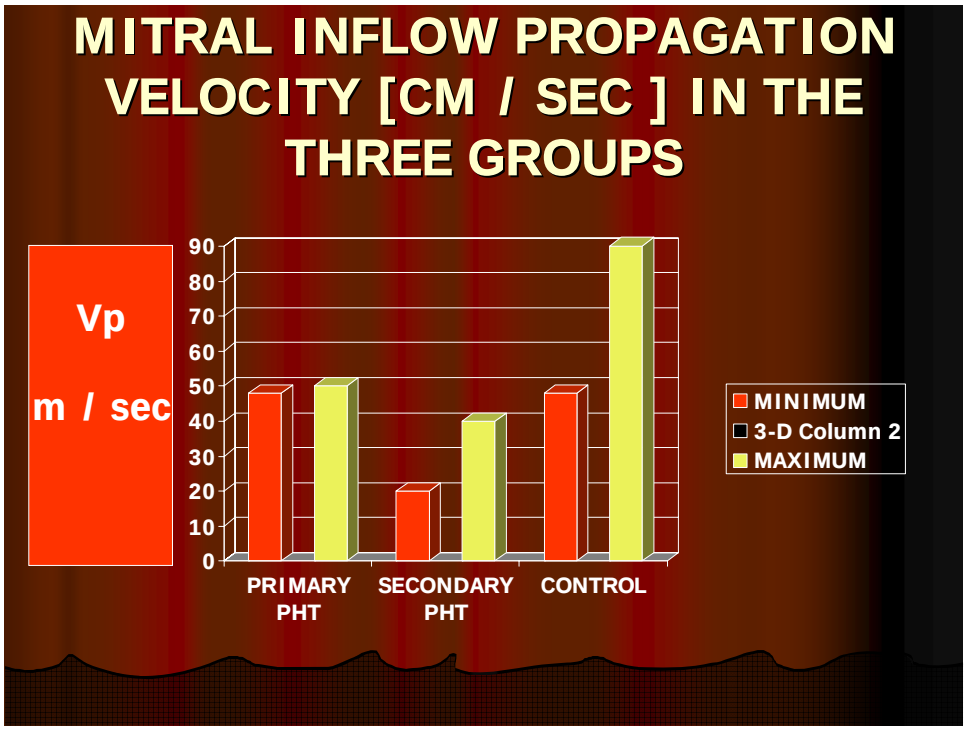
Normally, Vp is more than 50 cm / sec.

In GROUP A, Vp is in the range of 48 – 50 cm / sec.

In GROUP B, Vp is in the range of 20 – 40 cm / sec.

In GROUP C, Vp is kept in the normal range

	Vp (cm / sec)	MEAN	P Value
GROUP A	48 – 50	54	< 0.01
GROUP B	20 – 42	34	< 0.02
GROUP C	48 – 90	70	< 0.01



PULMONARY CAPILLARY WEDGE PRESSURE (mmHg):

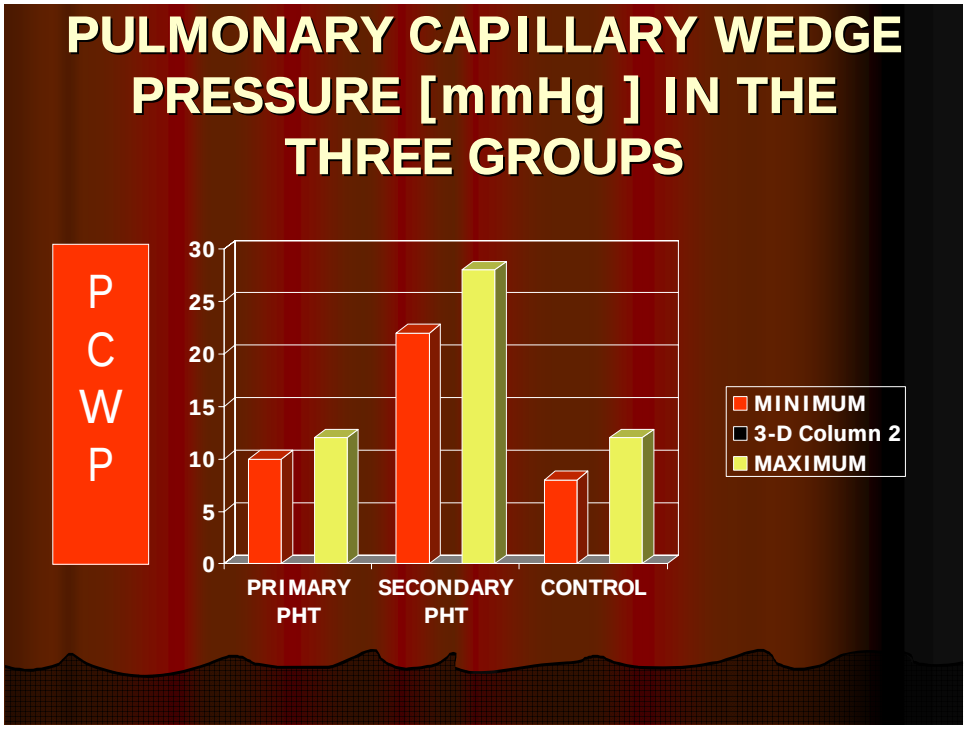
Normal PCWP is in the range of 8 – 12 mmHg.

In GROUP A, PCWP is in the range of 10 – 12 mmHg.

In GROUP B, PCWP is in the range of 22 – 26 mmHg.

In GROUP C, PCWP is kept in the normal range.

	PCWP (mmHg)	MEAN	P Value
GROUP A	10 – 12	11	< 0.01
GROUP B	22 – 26	24	< 0.02
GROUP C	7 – 12	9	< 0.01



MEAN PULMONARY ARTERY PRESSURE (MPAP) :

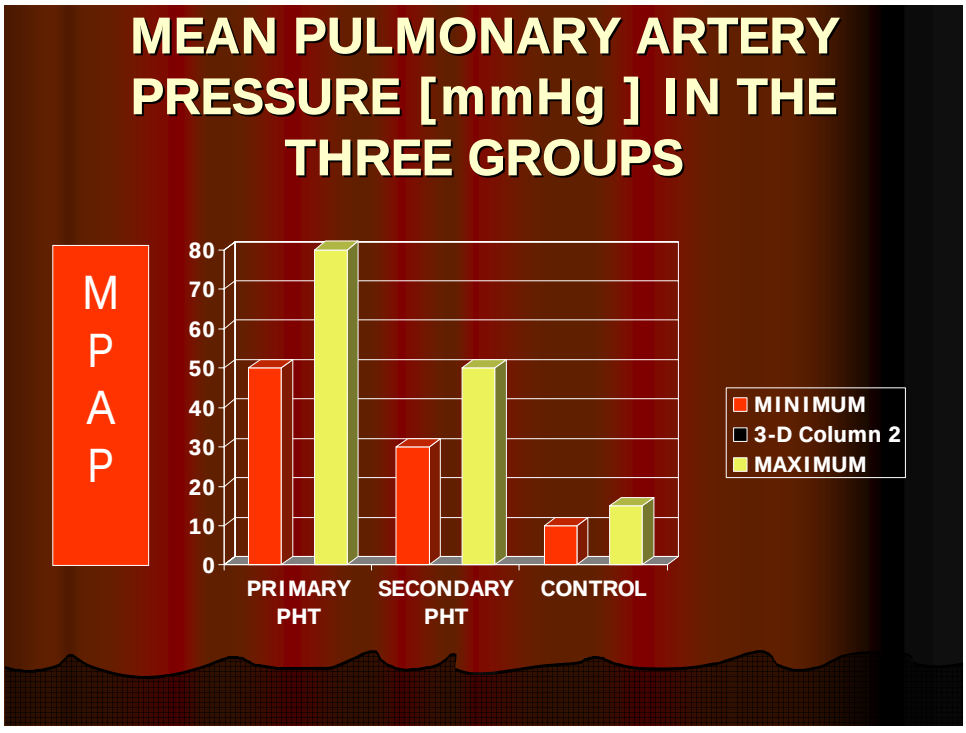
Normal MPAP is in the range of 10 – 15 mmHg.

In GROUP A, MPAP is in the range of 50 – 80 mmHg.

In GROUP B, MPAP is in the range of 30 – 50 mmHg.

In GROUP C, PCWP is kept in the normal range.

	MPAP (mmHg)	MEAN	P Value
GROUP A	50 -- 80	70	< 0.01
GROUP B	30 -- 50	42	< 0.02
GROUP C	10 -- 15	12	< 0.01



RV dP / dT : (mmHg / sec) :

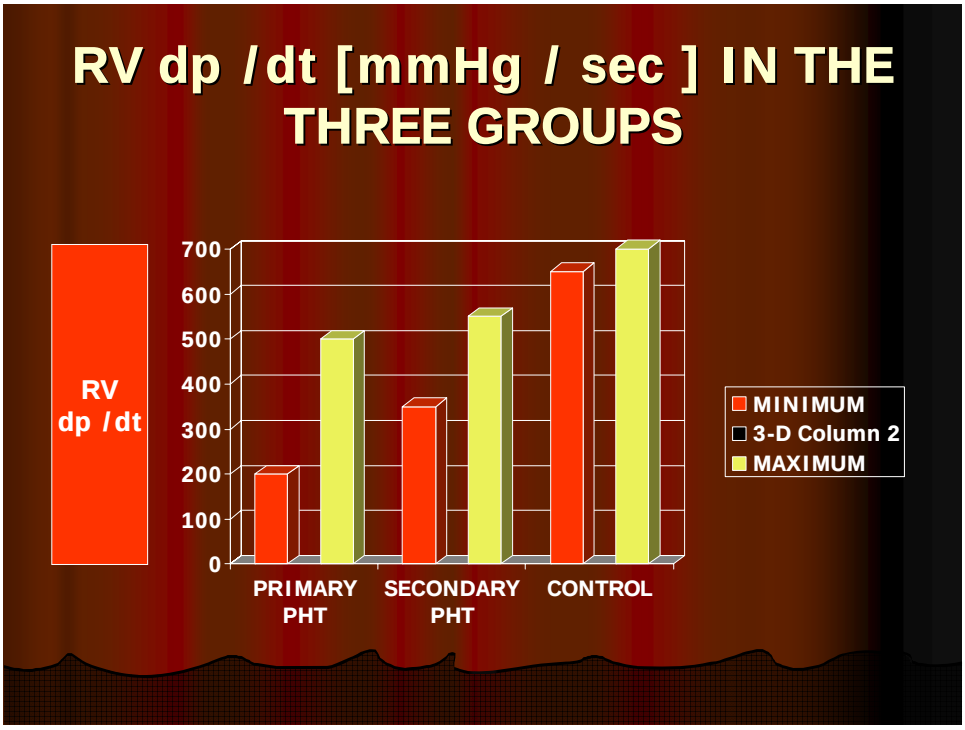
Normal RV dP / dT is in the range of 620 --740 .

In GROUP A, RV dP / dT is in the range of 200 – 500.

In GROUP B, RV dP / dT is in the range of 350 – 550.

In GROUP C, RV dP / dT is kept in the normal range.

	RV dP / dT : (mmHg / sec)	MEAN	P Value
GROUP A	200 -- 500	300	< 0.01
GROUP B	350 -- 550	450	< 0.02
GROUP C	660 -- 700	680	< 0.01



LV dP / dT : (mmHg / sec) :

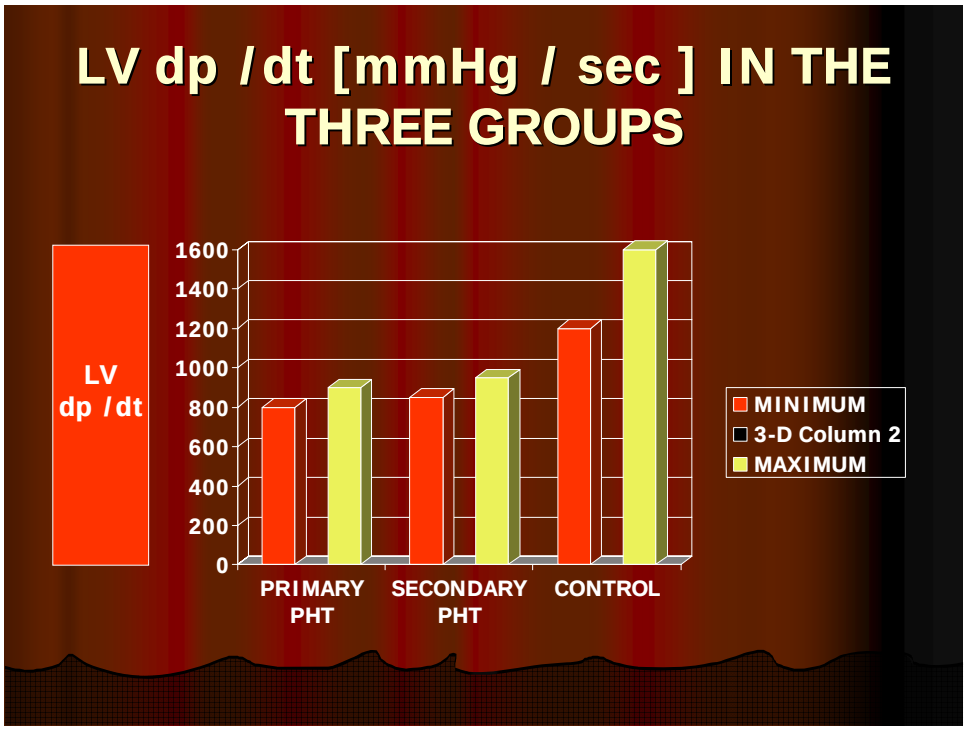
Normal LV dP / dT is in the range of 1000 -- 1600 .

In GROUP A, LV dP / dT is in the range of 800 – 900.

In GROUP B, LV dP / dT is in the range of 850 – 950.

In GROUP C, LV dP / dT is kept in the normal range.

	LV dP / dT : (mmHg / sec) :	MEAN	P Value
GROUP A	800 -- 900	850	< 0.01
GROUP B	850 -- 950	900	< 0.02
GROUP C	1200 -- 1600	1300	< 0.01



LVOT ACCELERATION

LVOT Acceleration was calculated in those cases without Mitral Regurgitation

NORMAL VALUE : MORE THAN 11 m/sec^2

	LVOT ACCELERATION	MEAN	P Value
GROUP A	10-12	11	< 0.01
GROUP B	10-14	12	< 0.02
GROUP C	12-14	13	< 0.01

DISCUSSION

MYOCARDIAL PERFORMANCE INDEX [MPI]
[TEI INDEX]

DEFINITION

- MPI (or Tei index) is defined as ratio of the sum of the isovolumic contraction time (IVCT) and isovolumic relaxation time (IVRT) divided by the systolic ejection time (ET)

$$MPI = \frac{IVCT + IVRT}{ET}$$

MPI = Myocardial Performance Index

IVCT = Isovolumic Contraction Time

IVRT = Isovolumic Relaxation Time

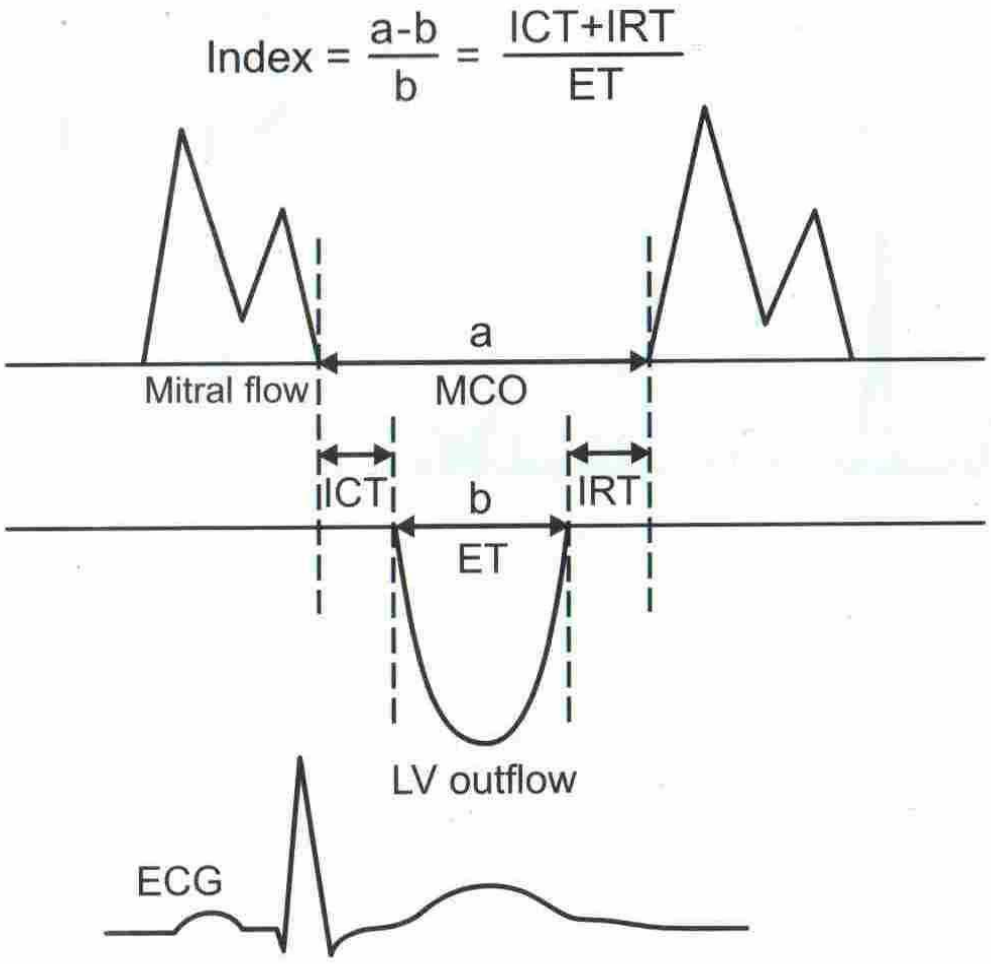


Diagram of mitral flow and left ventricular (*LV*) outflow tract flow for measuring various time intervals needed to calculate the Tei index. The combined time interval of isovolumic contraction time (*ICT*) and isovolumic relaxation time (*IRT*) is obtained by subtracting ejection time (*ET*) from mitral valve closure to opening (*MCO*). *ECG*, electrocardiogram.

NORMAL VALUES

- **LV MPI = LESS THAN 0.4**
- **RV MPI = LESS THAN 0.2**

MPI WITH TIME INTERVALS

- MPI is not limited by the geometric shape of the ventricle, a fact that is important in these patients who usually have distorted ventricular geometry.
- The MPI also includes changes of the IVRT, a diastolic time interval. The systolic and diastolic time intervals are easily obtained by routine Doppler techniques during standard echocardiographic examination and are simple to measure, with excellent reproducibility. In addition, MPI is independent of heart rate.

WHY RV MPI IS LESS THAN LV MPI

2 REASONS ARE SUGGESTED.:

- 1. RV IVRT is almost nonexistent. Since IVRT is present in the numerator aspect of TEI index the value of the fraction decreases.

- 2. As far as the inertia is concerned, RV has to pump blood against low impedence pulmonary vascular system.Hence,ejection time increases. Since ET is present in the denominator aspect of the TEI index,the value of the fraction decreases.[ACCORDING TO NEWTON"S FIRST LAW OF MOTION]

NEWTON"S FIRST LAW OF MOTION

- Every body continues in its state of rest or of motion until it is compelled by an external force acting on it.

This is called inertia as the corollary.

NEWTON"S SECOND LAW OF MOTION.

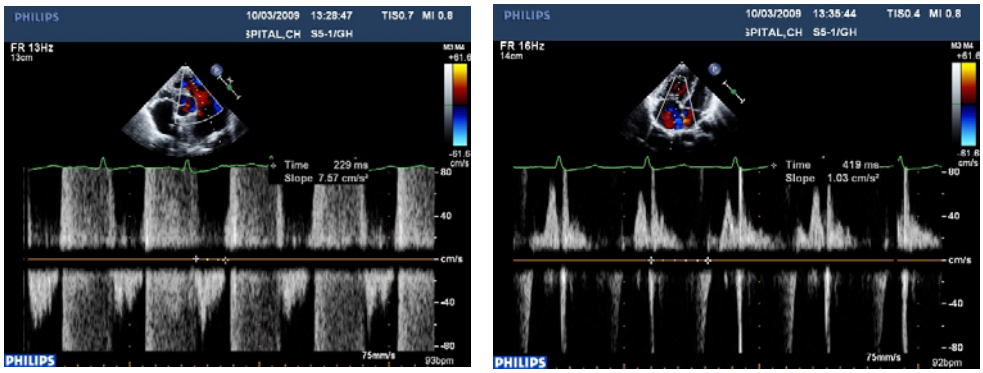
- The rate of change of momentum is directly proportional to the impressed force acting on it and takes part in the direction of the force

- Because of low impressed force,momentum decreases.

  So, velocity of blood decreases. Hence RV takes sufficient time to eject its blood. So, ejection time increases. Thereby,RV MPI decreases.

RV MPI

This is defined as ratio of the sum of the RV isovolumic contraction time (IVCT) and RV isovolumic relaxation time (IVRT) divided by the RV systolic ejection time (ET)



IVCT + IVRT = 190 msec

ET = 229 msec

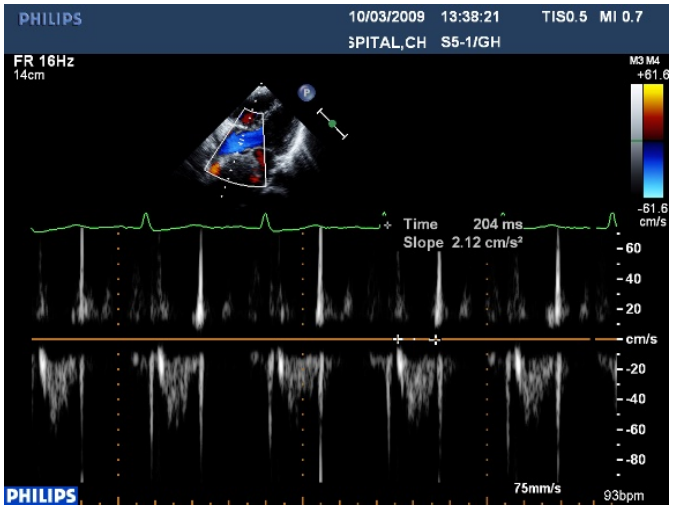
RV MPI = 190 / 229 = 0.86

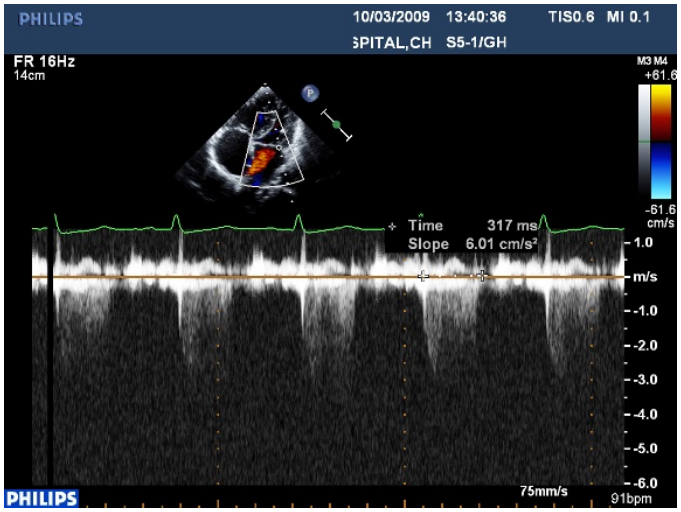
In primary PHT RV MPI was more than 0.7. The mean value 0.8 with a P Value of 0.01 which is statistically significant. In secondary PHT RV MPI was in the range of 0.3 to 0.4 with a mean value of 0.36 (P Value 0.02) which is also statically significant.

LV MPI

This is defined as ratio of the sum of the LV isovolumic contraction time (IVCT) and LV isovolumic relaxation time (IVRT) divided by the LV systolic ejection time (ET)

IVCT + IVRT = 113 msec
ET = 204 msec
LV MPI = 113 / 204 = 0.55



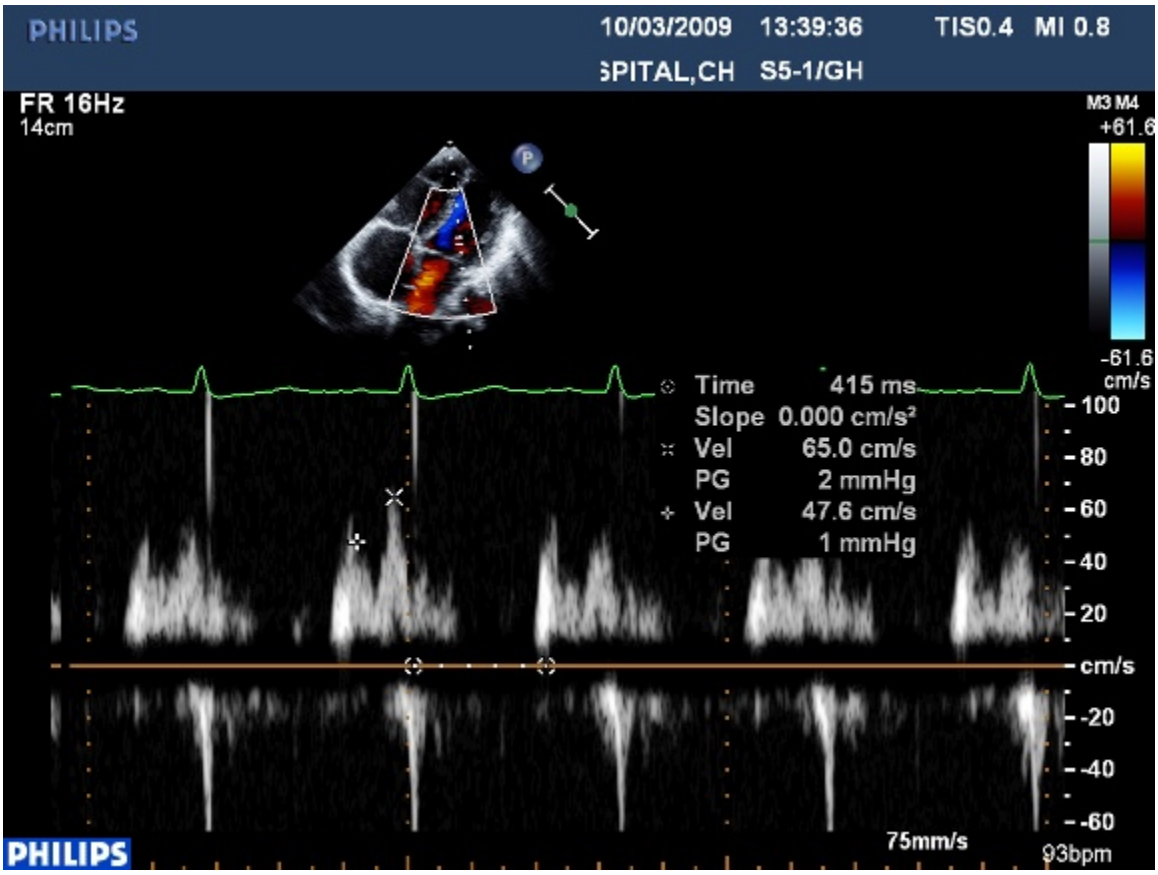


In both forms of PHT, LV MPI was within the normal range.

MITRAL E VELOCITY

This is calculated as follows.

The sample volume is kept in between the tips of the anterior and posterior mitral leaflets.Now,pulse Doppler of the mitral valve is displayed.The peak early diastolic filling velocity is calculated.This is called MITRAL E VELOCITY.



Here MITRAL E VELOCITY is 0.48 m / sec

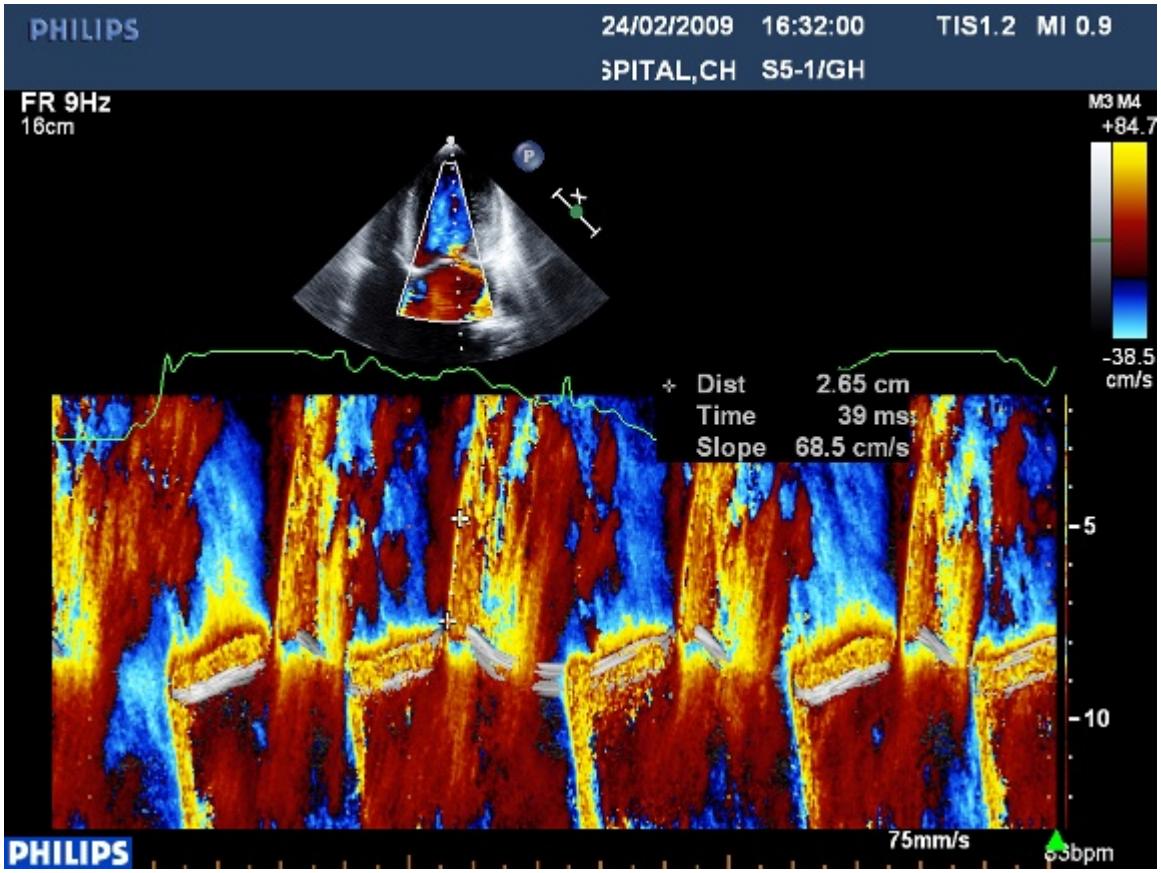
In Primary PHT it was 0.52 – 0.72m/sec. But in secondary PHT it was in the range of 0.7-1.6 m/sec. So in primary PHT, the diastolic function is affected more.

MITRAL INFLOW PROPAGATION VELOCITY [VP]

This is defined as the the tangent [slope] of the innermost colour spectrum of the mitral inflow jet when the sample volume is kept at 4 cm away from the mitral leaflets inside the LV cavity.

NORMAL VALUE :

MORE THAN 50 CM/SEC



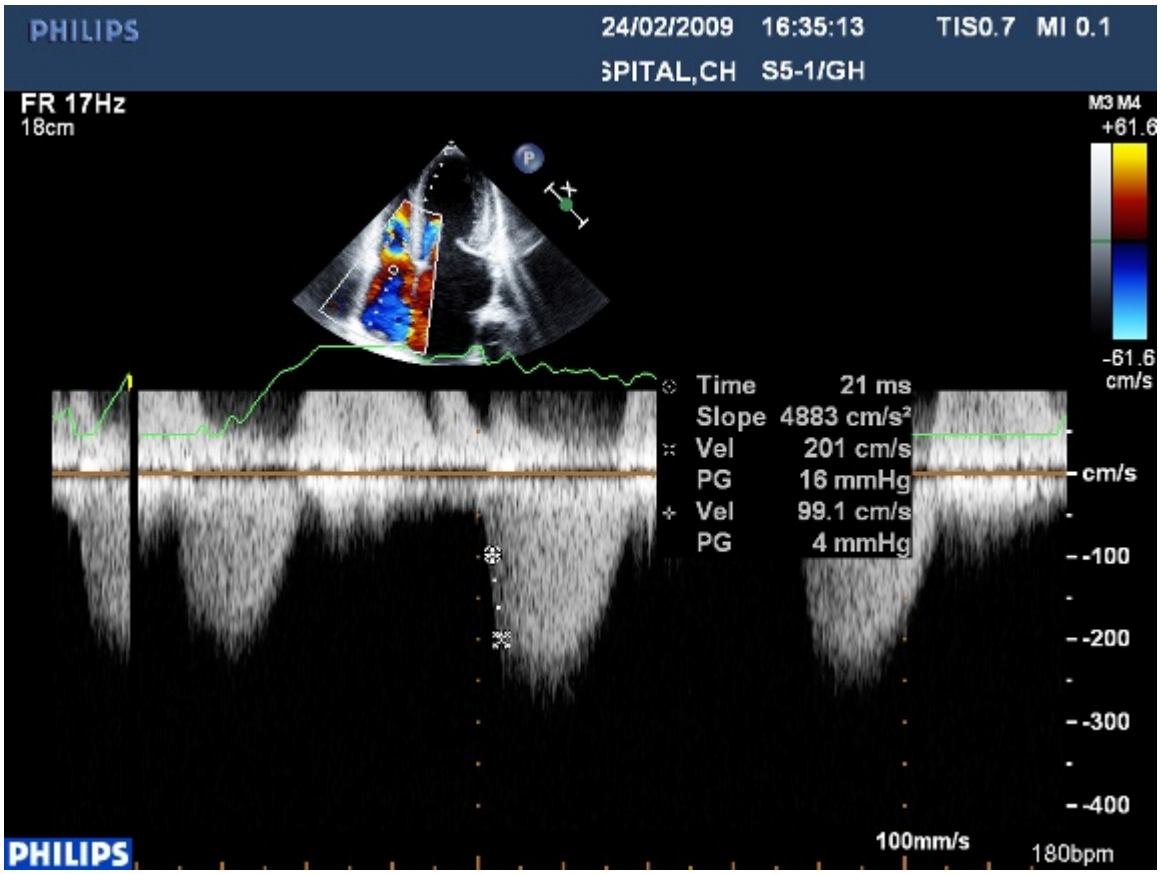
Here Vp is 68.5 cm / sec.

In primary PHT it was in the normal range. In secondary PHT it was grossly reduced.

RV dP / dT

- RV dP/dT was calculated from the TR jet.
- The change in pressure between 1m/sec and 2 m/sec was divided by the time interval between these two velocities.
- NORMAL VALUE :

680 +/- 60 mmHg/sec

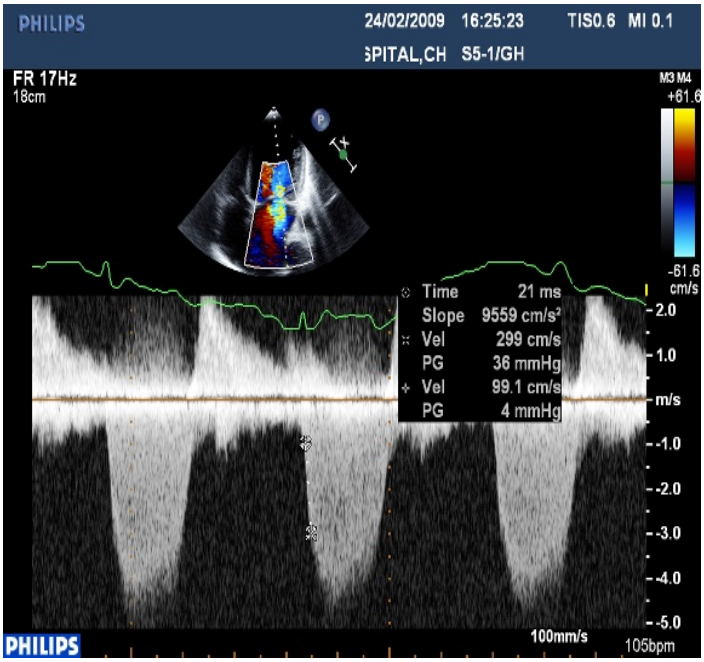


dP = 12 mmHg
dT = 21 msec
RV dP / dT = 12000 / 21 = 570 mmHg / sec

In primary PHT RV dP /dT was grossly affected. In Secondary PHT RV dP/dT was mildly affected. So RV dysfunction is more in primry PHT.

LV dP / dT

- This was calculated from the MR jet.
- The change in pressure between 1m/sec and 3m/sec was divided by the time interval between these two velocities
- Normal value :
- More than 1000 mmHg/sec
- 750 – 1000 mmHg/sec =mild LVD
- 500 – 750 mmHg/sec =moderate LVD
- Less than 500 mmHg/sec = severe



dP = 32 mmHg
dT = 21 msec
LV dP / dT = 32000 / 21 = 1524 mmHg / sec

In both forms of PHT, LV dP/dT was mildly reduced. So LV function is mildly reduced in both forms of PHT.

PULMONARY CAPILLARY WEDGE PRESSURE (PCWP)

PCWP was calculated by the following formula :

- **PCWP = [5.27 X E/Vp] + 4.6 (Ref. JK. OH-Manual)**
- **E = mitral E velocity**

  Vp = mitral inflow propagation velocity

- **The value is obtained in mmHg**

The PCWP is calculated by right heart heart catheterization.

For this, through the right femoral vein approach,the cournard catheter is inserted into the right femoral vein by modified Seldinger technique and positioned in the pulmonary capillary wedge.The mean value is obtained from 3recordings.

Pulmonary Capillary Wedge Pressure was within normal range in primary PHT. In secondary PHT it was elevated more than 22mmHg

MEAN PULMONARY ARTERY PRESSURE(MPAP)

MPAP was calculated as follows:

1. ALZEBRAIC METHOD :

$$MPAP = \frac{3[PAEDP] + PP}{3}$$

2. IN THE PRESENCE OF PR : [MASUYAMA]

$$MPAP = 4 \times [\text{PEAK PR VELOCITY}]^{2}$$

3. IN THE ABSENCE OF PR : [MAHAN]

$$MPAP = 0.79 - 0.45[\text{RVOT Act}]$$

4. SIMPLEST METHOD :

$$MPAP = 0.61 \times SPAP + 2$$

The MPAP was more than 50mmHg in Primary PHT. The MPAP was less than 50mmHg in Secondary PHT.

LVOT ACCELERATION (m/sec)

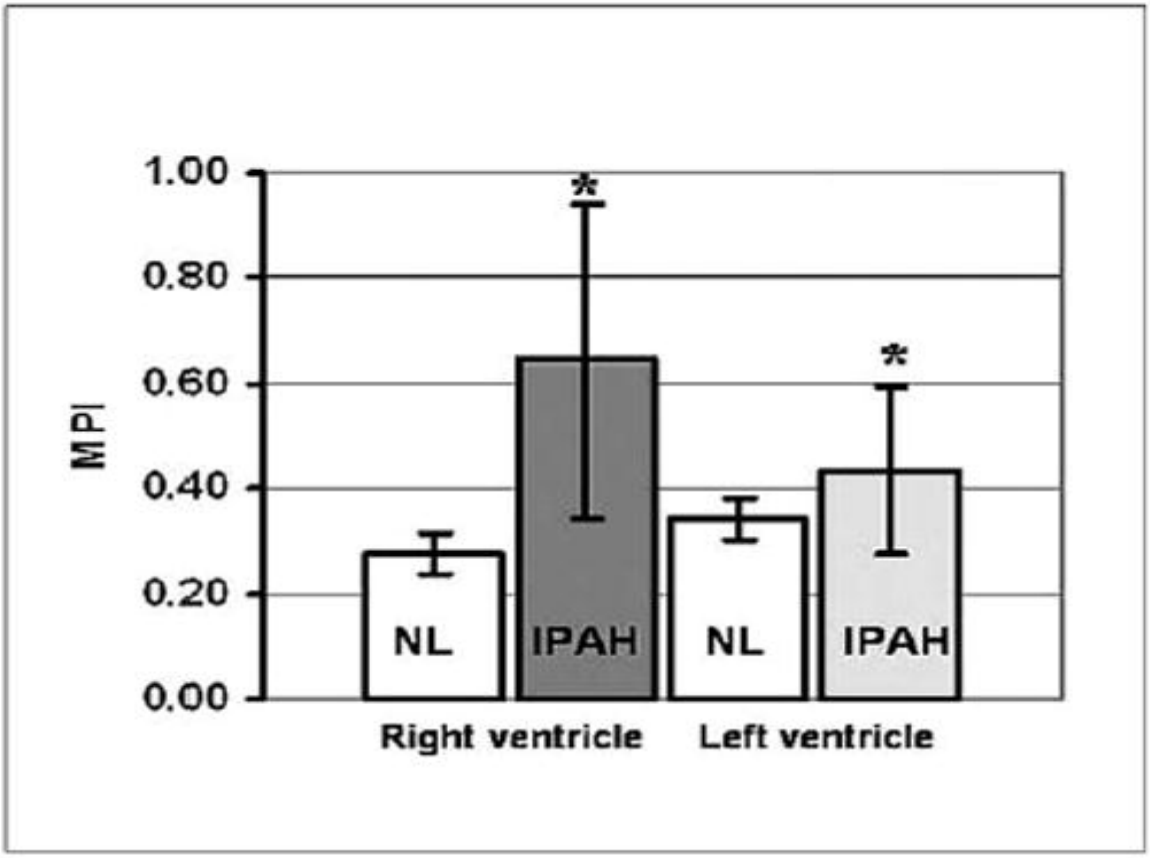
LVOT Acceleration was calculated in those cases without Mitral Regurgitation

NORMAL VALUE : MORE THAN 11 m/sec^2

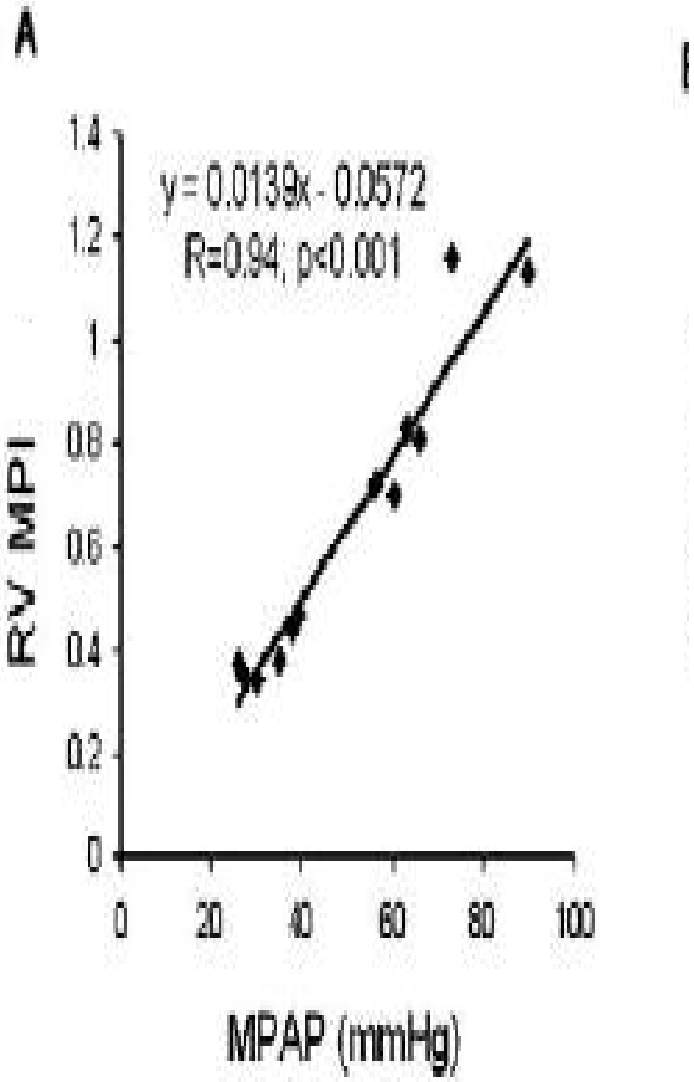
	LVOT ACCELERATION	MEAN	P Value
GROUP A	10-12	11	< 0.01
GROUP B	10-14	12	< 0.02
GROUP C	12-14	13	< 0.01

In both forms of PHT LVOT Acceleration was in the normal range.

DIFFERENCE BETWEEN RV MPI AND LV MPI IN PRIMARY PAH (*P < .05).



RV MPI CORRELATED WITH MPAP (*MPAP*)



CONCLUSION

RESULTS

- In primary pulmonary hypertension, RV MPI ranged from 0.6 to 1.0. But in secondary pulmonary hypertension, RV MPI ranged from 0.3 to 0.4.
- In primary pulmonary hypertension, pulmonary capillary wedge pressure is in the normal range. But in secondary pulmonary hypertension, pulmonary capillary wedge pressure was more than 22 mmHg.
- In primary pulmonary hypertension RV dp/dt decreases grossly. But in secondary pulmonary hypertension, RV dp/dt mildly decreases.
- In primary pulmonary hypertension, mean pulmonary artery pressure was above 50 mmHg. But in secondary pulmonary hypertension, mean pulmonary artery pressure was below 50mmHg.
- Primary pulmonary hypertension has major impact on diastolic dysfunction than secondary pulmonary hypertension.

BIBLIOGRAPHY

Journal of the American College of Cardiology HOME

D. B. Badesch, V. V. McLaughlin, M. Delcroix, C. Vizza, H. Olschewski, O. Sitbon, and R. J. Barst

Prostanoid therapy for pulmonary arterial hypertension

J. Am. Coll. Cardiol., June 16, 2004; 43(12_Suppl_S): 56S - 61S.

Journal of the American College of Cardiology HOME

H. A. Ghofrani, J. Pepke-Zaba, J. A. Barbera, R. Channick, A. M. Keogh, M. A. Gomez-Sanchez, M. Kneussl, and F. Grimminger

Nitric oxide pathway and phosphodiesterase inhibitors in pulmonary arterial hypertension

J. Am. Coll. Cardiol., June 16, 2004; 43(12_Suppl_S): 68S - 72S.

The Journal of THORACIC AND CARDIOVASCULAR SURGERY HOME

C. J. De Wet, D. G. Affleck, E. Jacobsohn, M. S. Avidan, H. Tymkew, L. L. Hill, P. B. Zanaboni, N. Moazami, and J. R. Smith

Inhaled prostacyclin is safe, effective, and affordable in patients with pulmonary hypertension, right heart dysfunction, and refractory hypoxemia after cardiothoracic surgery

J. Thorac. Cardiovasc. Surg., April 1, 2004; 127(4): 1058 - 1067.

European Respiratory Journal HOME

H.A. Ghofrani, G. Friese, T. Discher, H. Olschewski, R.T. Schermuly, N. Weissmann, W. Seeger, F. Grimminger, and J. Lohmeyer

Inhaled iloprost is a potent acute pulmonary vasodilator in HIV-related severe pulmonary hypertension

Eur. Respir. J., February 1, 2004; 23(2): 321 - 326.

CHEST HOME

H. H. Leuchte, M. Schwaiblmair, R. A. Baumgartner, C. F. Neurohr, T. Kolbe, and J. Behr

Hemodynamic Response to Sildenafil, Nitric Oxide, and Iloprost in Primary Pulmonary Hypertension

Chest, February 1, 2004; 125(2): 580 - 586.

CHEST HOME

H. Olschewski, B. Rohde, J. Behr, R. Ewert, T. Gessler, H. A. Ghofrani, and T. Schmehl

Pharmacodynamics and Pharmacokinetics of Inhaled Iloprost, Aerosolized by Three Different Devices, in Severe Pulmonary Hypertension

Chest, October 1, 2003; 124(4): 1294 - 1304.

Mayo Clinic Proceedings HOME

S. Bhatia, R. P. Frantz, C. J. Severson, L. A. Durst, and M. D. McGoon

Immediate and Long-term Hemodynamic and Clinical Effects of Sildenafil in Patients With Pulmonary Arterial Hypertension Receiving Vasodilator Therapy

Mayo Clin. Proc., October 1, 2003; 78(10): 1207 - 1213.

THE ANNALS OF THORACIC SURGERY HOME

T. Kramm, B. Eberle, F. Krummenauer, S. Guth, H. Oelert, and E. Mayer

Inhaled iloprost in patients with chronic thromboembolic pulmonary hypertension: effects before and after pulmonary thromboendarterectomy

Ann. Thorac. Surg., September 1, 2003; 76(3): 711 - 718.

Annals of Internal Medicine HOME

H.H Leuchte, R.A Baumgartner, and J Behr

Treatment of Severe Pulmonary Hypertension with Inhaled Iloprost

Ann Intern Med, August 19, 2003; 139(4): 306 - 306.

European Respiratory Journal HOME

R.T. Schermuly, H. Leuchte, H.A. Ghofrani, N. Weissmann, F. Rose, M. Kohstall, H. Olschewski, C. Schudt, F. Grimminger, W. Seeger, *et al.*

Zardaverine and aerosolised iloprost in a model of acute respiratoryfailure

Eur. Respir. J., August 1, 2003; 22(2): 342 - 347.

ANESTHESIA & ANALGESIA HOME

G. Stratmann and G. A. Gregory

Neurogenic and Humoral Vasoconstriction in Acute Pulmonary Thromboembolism

Anesth. Analg., August 1, 2003; 97(2): 341 - 354.

Journal of the American College of Cardiology HOME

H. A. Ghofrani, F. Rose, R. T. Schermuly, H. Olschewski, R. Wiedemann, A. Kreckel, N. Weissmann, S. Ghofrani, B. Enke, W. Seeger, *et al.*

Oral sildenafil as long-term adjunct therapy to inhaled iloprost in severe pulmonary arterial hypertension

J. Am. Coll. Cardiol., July 2, 2003; 42(1): 158 - 164.

CHEST HOME

F. M. Fruhwald, B. Kjellstrom, W. Perthold, N. Watzinger, R. Maier, P. A. Grandjean, and W. Klein

Continuous Hemodynamic Monitoring in Pulmonary Hypertensive Patients Treated With Inhaled Iloprost

Chest, July 1, 2003; 124(1): 351 - 359.

ANESTHESIA & ANALGESIA HOME

L. G. Fischer, H. V. Aken, and H. Burkle

Management of Pulmonary Hypertension: Physiological and Pharmacological Considerations for Anesthesiologists

Anesth. Analg., June 1, 2003; 96(6): 1603 - 1616.

ANESTHESIA & ANALGESIA HOME

A. Martineau, G. Arcand, P. Couture, D. Babin, L. P. Perreault, and A. Denault

Transesophageal Echocardiographic Diagnosis of Carbon Dioxide Embolism During Minimally Invasive Saphenous Vein Harvesting and Treatment with Inhaled Epoprostenol

Anesth. Analg., April 1, 2003; 96(4): 962 - 964.

The Journal of THORACIC AND CARDIOVASCULAR SURGERY HOME

M. Hache, A. Denault, S. Belisle, D. Robitaille, P. Couture, P. Sheridan, M. Pellerin, D. Babin, N. Noel, M.-C. Guertin, *et al.*

Inhaled epoprostenol (prostacyclin) and pulmonary hypertension before cardiac surgery

J. Thorac. Cardiovasc. Surg., March 1, 2003; 125(3): 642 - 649.

European Heart Journal HOME

C.F Opitz, R Wensel, M Bettmann, R Schaffarczyk, M Linscheid, R Hetzer, and R Ewert

Assessment of the vasodilator response in primary pulmonary hypertension: Comparing prostacyclin and iloprost administered by either infusion or inhalation

Eur. Heart J., February 2, 2003; 24(4): 356 - 365.

Canadian Journal of Anesthesia HOME

A. Sablotzki, E. Czeslick, S. Schubert, I. Friedrich, J. Muhling, M. G. Dehne, S. Grond, and T. Hentschel

Iloprost improves hemodynamics in patients with severe chronic cardiac failure and secondary pulmonary hypertension: [L'iloprost ameliore l'hemodynamique chez des malades souffrant d'insuffisance cardiaque chronique et d'hypertension arterielle pulmonaire]

Can J Anesth, December 1, 2002; 49(10): 1076 - 1080.

EUROPEAN JOURNAL OF CARDIO-THORACIC SURGERY HOME

A. Sablotzki, T. Hentschel, E. Gruenig, S. Schubert, I. Friedrich, J. Muhling, M. G. Dehne, and E. Czeslick

Hemodynamic effects of inhaled aerosolized iloprost and inhaled nitric oxide in heart transplant candidates with elevated pulmonary vascular resistance

Eur. J. Cardiothorac. Surg., November 1, 2002; 22(5): 746 - 752.

JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS HOME

R. T. Schermuly, A. Schulz, H. A. Ghofrani, A. Meidow, F. Rose, A. Roehl, N. Weissmann, M. Hildebrand, J. Kurz, F. Grimminger, *et al.*

Pharmacokinetics and Metabolism of Infused versus Inhaled Iloprost in Isolated Rabbit Lungs

J. Pharmacol. Exp. Ther., November 1, 2002; 303(2): 741 - 745.

European Respiratory Journal HOME

N. Galie, A. Manes, and A. Branzi

The new clinical trials on pharmacological treatment in pulmonary arterial hypertension

Eur. Respir. J., October 1, 2002; 20(4): 1037 - 1049.

European Respiratory Journal HOME

M.M. Hoeper, E. Spiekerkoetter, V. Westerkamp, R. Gatzke, and H. Fabel

Intravenous iloprost for treatment failure of aerosolised iloprost in pulmonary arterial hypertension

Eur. Respir. J., August 1, 2002; 20(2): 339 - 343.

The NEW ENGLAND JOURNAL of MEDICINE HOME

H. Olschewski, G. Simonneau, N. Galie, T. Higenbottam, R. Naeije, L. J. Rubin, S. Nikkho, R. Speich, M. M. Hoeper, J. Behr, *et al.*

Inhaled Iloprost for Severe Pulmonary Hypertension

N. Engl. J. Med., August 1, 2002; 347(5): 322 - 329.

Lupus HOME

E Mcmillan, W L Martin, J Waugh, I Rushton, M Lewis, T Clutton-Brock, J N Townend, M D Kilby, and C Gordon

Management of pregnancy in women with pulmonary hypertension secondary to SLE and anti-phospholipid syndrome

Lupus, June 1, 2002; 11(6): 392 - 398.

CHEST HOME

F. C. Blumberg, G. A. J. Riegger, and M. Pfeifer

Hemodynamic Effects of Aerosolized Iloprost in Pulmonary Hypertension at Rest and During Exercise*

Chest, May 1, 2002; 121(5): 1566 - 1571.

AMERICAN JOURNAL OF Respiratory and Critical Care Medicine HOME

M. M. Hoeper, N. Galie, G. Simonneau, and L. J. Rubin

New Treatments for Pulmonary Arterial Hypertension

Am. J. Respir. Crit. Care Med., May 1, 2002; 165(9): 1209 - 1216.

Annals of Internal Medicine HOME

H. A. Ghofrani, R. Wiedemann, F. Rose, H. Olschewski, R. T. Schermuly, N. Weissmann, W. Seeger, and F. Grimminger

Combination Therapy with Oral Sildenafil and Inhaled Iloprost for Severe Pulmonary Hypertension

Ann Intern Med, April 2, 2002; 136(7): 515 - 522.

GLOSSARY AND ACRONYMS

PHT -- Pulmonary Hypertension

IPAH -- Idiopathic Pulmonary Arterial Hypertension

MPAP – Mean Pulmonary Artery Pressure

SPAP -- Systolic Pulmonary Artery Pressure

PAOP – Pulmonary Artery Occlusion Pressure

PCWP – Pulmonary Capillary Wedge Pressure

MPI -- Myocardial Performance Index

PVR -- Pulmonary Vascular Resistance

COPD – Chronic Obstructive Pulmonary Disease

c GMP – cyclic Guanosine Monophosphate

PDE 5 -- Phospho Diesterase inhibitor 5

5HTT -- 5 Hydroxy Tryptamine Transporter

BMPR2 -- Bone Morphogenetic Protein Receptor type 2 gene

BNP -- Brain Natriuretic Peptide

TGF-b -- Transforming Growth Factor beta

FPAH – Familial Pulmonary Arterial Hypertension

GROUP A :PRIMARY PULMONARY HYPERTENSION

NAME	AGE	SEX	SMOKER	ALCOHOLIC	DIABETIC	HIGH BP	RV MPI	LV MPI	E VELOCITY cm	Vp cm	PCWP mm Hg	MPAP mm Hg	RV DP/DT mm Hg / sec	LV DP/DT Mm Hg / sec	DIASTOLIC DYSFUNCTION GRADES
NAGAN	20	M	YES	YES	N	N	0.70	0.42	60	60	7	10	260	825	1
LAKSHMI	22	F	NO	NO	N	N	0.82	0.44	66	58	12	10.5	300	850	3
KALA	24	F	NO	NO	N	N	0.92	0.42	65	52	7	10.5	500	800	1
NEHRU	10	M	YES	NO	Y	Y	0.96	0.48	63	72	11	10.5	200	900	2
BAMA	25	F	NO	NO	N	N	0.74	0.46	66	60	8	11	400	810	2
RUKMANI	16	F	NO	NO	N	N	0.72	0.46	66	58	11	11.5	450	870	1
MAYEE	14	F	NO	NO	N	N	0.88	0.44	69	59	8	10.5	350	880	2
NAGALA	14	F	NO	NO	N	N	0.84	0.45	70	60	10	11.5	400	850	1
SOUNDRA	18	F	NO	NO	N	N	0.77	0.47	64	56	9	12	300	840	1
REKA	20	F	NO	NO	N	N	0.76	0.46	62	54	10	12	250	900	1

GROUP B : SECONDARY PULMONARY HYPERTENSION

NAME	AGE	SEX	SMOKER	ALCOHOLIC	DIABETIC	HIGH BP	RV MPI	LV MPI	E VELOCITY cm	Vp cm	PCWP mm Hg	MPAP mm Hg	RV DP/DT mm Hg / sec	LV DP/DT nm Hg / sec	DIASTOLIC DYSFUNCTION GRADES
RAJ	30	M	YES	NO	N	N	0.32	0.40	70	42	22	30	350	850	1
MALA	22	F	NO	NO	N	N	0.35	0.46	160	20	26	32	350	860	NO
ASHOK	44	M	YES	NO	Y	Y	0.36	0.41	75	38	23	34	400	870	NO
MARY	26	F	NO	NO	N	N	0.34	0.45	93	25	25	36	400	880	NO
RAGU	48	M	NO	NO	N	N	0.32	0.42	76	30	24	38	450	890	NO
GEETHA	40	F	NO	NO	N	N	0.38	0.44	146	40	22	40	450	900	NO
SEKAR	46	M	YES	NO	N	N	0.38	0.45	98	40	22	42	500	910	NO
STELLA	44	F	NO	NO	Y	Y	0.39	0.46	94	38	22	44	500	920	NO
AKBAR	48	M	YES	NO	N	Y	0.40	0.40	74	20	26	46	550	930	NO
BEEVI	50	F	NO	NO	Y	Y	0.35	0.46	150	20	26	48	550	940	NO

NAME	AGE	SEX	SMOKER	ALCOHOLIC	DIABETIC	HIGH BP	RV MPI	LV MPI	E VELOCITY cm	Vp cm	PCWP mm Hg	MPAP mm Hg	RV DP/DT mm Hg / sec	LV DP/DT nm Hg / sec	DIASTOLIC DYSFUNCTION GRADES
KHAN	40	M	YES	NO	Y	Y	0.31	0.41	70	21	26	50	350	950	NO
BANU	32	F	NO	NO	N	N	0.33	0.45	96	28	23	48	400	950	NO
VICTOR	34	M	YES	NO	N	N	0.35	0.42	75	30	23	46	450	940	NO
RANI	36	F	NO	NO	N	N	0.37	0.43	83	27	23	44	500	930	NO
GOVINDA	48	M	YES	NO	N	N	0.39	0.44	96	24	25	42	550	920	NO
SANTHA	46	F	NO	NO	N	N	0.30	0.40	76	24	25	40	500	910	NO
KUPPU	54	M	YES	NO	N	N	0.32	0.40	70	25	25	38	450	900	NO
VALLI	44	F	NO	NO	Y	N	0.34	0.46	156	30	24	36	400	890	NO
NAGUBAI	48	F	NO	NO	N	N	0.36	0.46	160	28	24	34	350	880	NO
LALU	50	M	YES	NO	Y	Y	0.38	0.41	72	32	24	32	550	870	NO

NAME	AGE	SEX	SMOKER	ALCOHOLIC	DIABETIC	HIGH BP	RV MPI	LV MPI	E VELOCITY cm	Vp cm	PCWP mm Hg	MPAP mm Hg	RV DP/DT mm Hg / sec	LV DP/DT nm Hg / sec	DIASTOLIC DYSFUNCTION GRADES
RAVI	40	M	YES	YES	N	N	0.40	0.41	80	42	22	30	350	860	1
BALU	32	M	YES	YES	N	N	0.38	0.45	96	40	22	31	450	850	NO
RAMAN	44	M	YES	YES	N	N	0.36	0.45	95	42	22	32	550	850	NO
JAYARAM	36	M	YES	YES	Y	Y	0.34	0.42	73	40	22	33	400	860	NO
KARTHIK	38	M	YES	YES	N	N	0.32	0.42	76	20	26	34	500	870	NO
SRIRAM	36	M	YES	YES	N	N	0.30	0.44	86	22	26	35	550	880	NO
SRINIVAS	40	M	YES	YES	N	N	0.31	0.44	109	24	26	36	450	890	NO
BASKAR	44	M	YES	YES	Y	Y	0.33	0.43	80	23	26	37	350	900	NO
SUBBU	48	M	YES	YES	N	Y	0.35	0.43	84	36	23	38	400	910	NO
JUSTIN	50	M	YES	YES	N	Y	0.37	0.40	72	38	23	39	500	920	1

NAME	AGE	SEX	SMOKER	ALCOHOLIC	DIABETIC	HIGH BP	RV MPI	LV MPI	E VELOCITY cm	Vp cm	PCWP mm Hg	MPAP mm Hg	RV DP/DT mm Hg / sec	LV DP/DT nm Hg / sec	DIASTOLIC DYSFUNCTION GRADES
JACOB	30	M	NO	NO	N	N	0.39	0.40	70	38	23	40	350	930	1
KUMAR	32	M	NO	NO	N	N	0.31	0.41	76	34	23	41	450	940	NO
SANTHI	34	F	NO	NO	N	N	0.30	0.41	75	26	25	42	550	950	NO
HEMA	26	F	NO	NO	N	N	0.39	0.42	73	24	25	43	500	950	NO
DEVI	28	F	NO	NO	N	N	0.32	0.42	76	25	25	44	400	930	NO
DHANAM	36	F	NO	NO	N	N	0.38	0.43	86	26	25	45	550	910	NO
JANAKI	40	F	NO	NO	N	N	0.33	0.43	79	32	24	46	450	890	NO
MANGAI	44	F	NO	NO	N	N	0.37	0.44	90	34	24	47	350	870	NO
DEVIKA	48	F	NO	NO	Y	Y	0.34	0.44	94	33	24	48	400	850	NO
PADMINI	50	F	NO	NO	Y	Y	0.36	0.45	132	34	24	49	500	950	1

GROUP C : CONTROL POPULATION

NAME	AGE	SEX	SMOKER	ALCOHOLIC	DIABETIC	HIGH BP	RV MPI	LV MPI	E VELOCITY cm	Vp cm	PCWP mm Hg	MPAP mm Hg	RV DP/DT mm Hg / sec	LV DP/DT nm Hg / sec	DIASTOLIC DYSFUNCTION GRADES
NAGU	20	M	YES	YES	N	N	0.12	0.26	60	48	7	10	660	1200	NO
JEYA	22	F	NO	NO	N	N	0.12	0.34	66	54	12	15	665	1600	NO
SAKILA	24	F	NO	NO	N	N	0.12	0.34	65	56	7	14.5	670	1250	NO
JAWAL	26	M	NO	NO	Y	Y	0.18	0.36	63	50	11	10.5	700	1550	NO
GOVIND	28	M	YES	NO	N	N	0.18	0.35	66	90	8	14	675	1300	NO
MANI	36	M	NO	NO	N	N	0.16	0.3	66	58	11	11	680	1500	NO
JOTHI	40	F	NO	NO	N	N	0.15	0.29	69	59	8	13.5	685	1350	NO
AMMAL	44	F	NO	NO	Y	N	0.14	0.28	70	60	10	11.5	680	1400	NO
VALLI	48	F	NO	NO	N	Y	0.17	0.27	64	56	9	13	685	1450	NO
KUPPU	50	M	NO	NO	N	Y	0.16	0.26	62	54	10	12	695	1600	NO